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(54) Title: COMBINATION COMPRISING A STAUROSPORINE AND A CYP3A4 INHIBITOR

(57) Abstract: The present invention relates to a method of treating myelodysplastic syndromes, lymphomas and leukemias and solid tumors in mammals with a pharmaceutical combination of a Staurosporine Derivative and a CYP3A4 inhibitor. It also relates to the use of a pharmaceutical combination of a CYP3A4 inhibitor and a FLT-3 kinase inhibitor for the treatment of the diseases or malignancies mentioned above and the use of such a pharmaceutical composition for the manufacture of a medicament for the treatment of these diseases or malignancies.



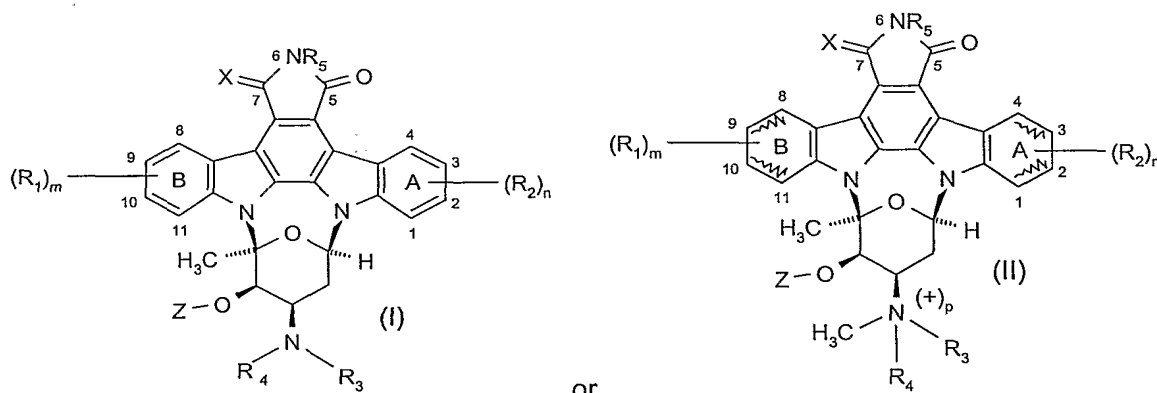
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COMBINATION COMPRISING A STAUROSPORINE AND A CYP3A4 INHIBITOR

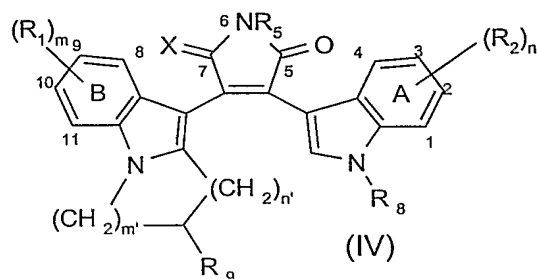
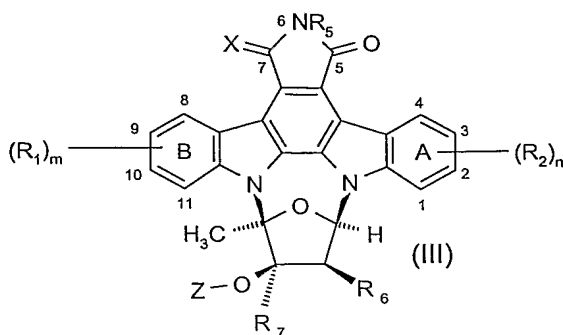
The present invention relates to a method of treating allergic rhinitis, allergic dermatitis, drug allergy or food allergy, angioedema, urticaria, sudden infant death syndrome, bronchopulmonary aspergillosis, multiple sclerosis, or mastocytosis with a pharmaceutical combination of a STAUROSPORINE DERIVATIVE and a CYP3A4 inhibitor. It also relates to the use of a pharmaceutical combination of a CYP3A4 inhibitor and a FLT-3 kinase inhibitor for the treatment of the diseases or malignancies mentioned above and the use of such a pharmaceutical composition for the manufacture of a medicament for the treatment of these diseases or malignancies.

It has now surprisingly been found that a STAUROSPORINE DERIVATIVE in combination with a CYP3A4 inhibitor possess therapeutic properties, which render them particularly useful for the treatment allergic rhinitis, allergic dermatitis, drug allergy or food allergy, angioedema, urticaria, sudden infant death syndrome, bronchopulmonary aspergillosis, multiple sclerosis, or mastocytosis .

STAUROSPORINE DERIVATIVES of particular interest for use in the inventive combination are staurosporine derivatives of formula

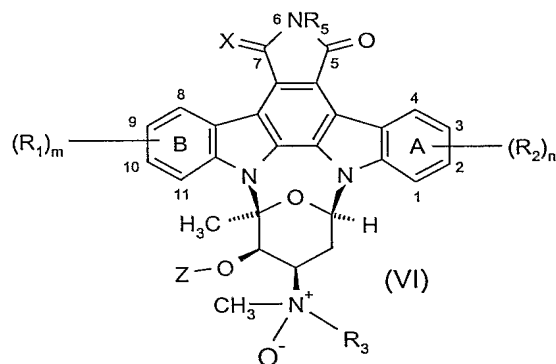
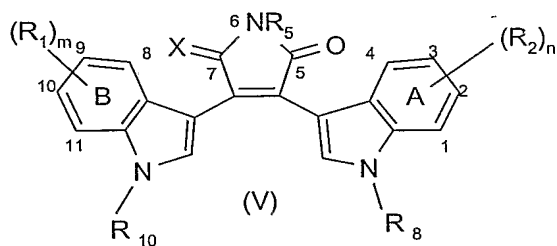


wherein (II) is the partially hydrogenated derivative of compound (I),



or

or



or

or

wherein R_1 and R_2 , are, independently of one another, unsubstituted or substituted alkyl, hydrogen, halogen, hydroxy, etherified or esterified hydroxy, amino, mono- or disubstituted amino, cyano, nitro, mercapto, substituted mercapto, carboxy, esterified carboxy, carbamoyl, N-mono- or N,N-di-substituted carbamoyl, sulfo, substituted sulfonyl, aminosulfonyl or N-mono- or N,N-di-substituted aminosulfonyl;

n and m are, independently of one another, a number from and including 0 to and including 4;
 n' and m' are, independently of one another, a number from and including 0 to and including 4;

R₃, R₄, R₈ and R₁₀ are, independently of one another, hydrogen, -O⁻, acyl with up to 30 carbon atoms, an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms in each case, a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms in each case, and in each case up to 9 heteroatoms, an acyl with up to 30 carbon atoms, wherein R₄ may also be absent;

or if R₃ is acyl with up to 30 carbon atoms, R₄ is not an acyl;

p is 0 if R₄ is absent, or is 1 if R₃ and R₄ are both present and in each case are one of the aforementioned radicals;

R₅ is hydrogen, an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms in each case, or a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms in each case, and in each case up to 9 heteroatoms, or acyl with up to 30 carbon atoms;

R₇, R₈ and R₉ are acyl or -(lower alkyl) -acyl, unsubstituted or substituted alkyl, hydrogen, halogen, hydroxy, etherified or esterified hydroxy, amino, mono- or disubstituted amino, cyano, nitro, mercapto, substituted mercapto, carboxy, carbonyl, carbonyldioxy, esterified carboxy, carbamoyl, N-mono- or N,N-di-substituted carbamoyl, sulfo, substituted sulfonyl, aminosulfonyl or N-mono- or N,N-di-substituted aminosulfonyl;

X stands for 2 hydrogen atoms; for 1 hydrogen atom and hydroxy; for O; or for hydrogen and lower alkoxy;

Z stands for hydrogen or lower alkyl;

and either the two bonds characterised by wavy lines are absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present.

The general terms and definitions used hereinbefore and hereinafter preferably have the following meanings for the staurosporine derivatives:

The prefix "lower" indicates that the associated radical preferably has up to and including a maximum of 7 carbon atoms, especially up to and including a maximum of 4 carbon atoms.

Lower alkyl is especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, or tert-butyl, and also pentyl, hexyl, or heptyl.

Unsubstituted or substituted alkyl is preferably C₁-C₂₀alkyl, especially lower alkyl, typically methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, or tert-butyl, which is unsubstituted or substituted especially by halogen, such as fluorine, chlorine, bromine, or iodine, C₆-C₁₄aryl, such as phenyl or naphthyl, hydroxy, etherified hydroxy, such as lower alkoxy, phenyl-lower alkoxy or phenyloxy, esterified hydroxy, such as lower alkanoyloxy or benzoyloxy, amino, mono- or disubstituted amino, such as lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, substituted mercapto, such as lower alkylthio, carboxy, esterified carboxy, such as lower alkoxycarbonyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, such as N-lower alkylcarbamoyl or N,N-di-lower alkylcarbamoyl, sulfo, substituted sulfo, such as lower alkanesulfonyl or lower alkoxy sulfonyl, aminosulfonyl or N-mono- or N,N-disubstituted aminosulfonyl, such as N-lower alkylaminosulfonyl or N,N-di-lower alkylaminosulfonyl.

Halogen is preferably fluorine, chlorine, bromine, or iodine, especially fluorine or chlorine.

Etherified hydroxy is especially lower alkoxy, C₆-C₁₄aryloxy, such as phenyloxy, or C₆-C₁₄aryl-lower alkoxy, such as benzyloxy.

Esterified hydroxy is preferably lower alkanoyloxy or C₆-C₁₄arylcarbonyloxy, such as benzoyloxy.

Mono- or disubstituted amino is especially amino monosubstituted or disubstituted by lower

alkyl, C₆-C₁₄aryl, C₆-C₁₄aryl-lower alkyl, lower alkanoyl, or C₆-C₁₂arylcarbonyl.

Substituted mercapto is especially lower alkylthio, C₆-C₁₄arylthio, C₆-C₁₄aryl-lower alkylthio, lower alkanoylthio, or C₆-C₁₄aryl-lower alkanoylthio.

Esterified carboxy is especially lower alkoxycarbonyl, C₆-C₁₄aryl-lower alkoxycarbonyl or C₆-C₁₄aryloxycarbonyl.

N-Mono- or N,N-disubstituted carbamoyl is especially carbamoyl N-monosubstituted or N,N-disubstituted by lower alkyl, C₆-C₁₄aryl or C₆-C₁₄aryl-lower alkyl.

Substituted sulfonyl is especially C₆-C₁₄arylsulfonyl, such as toluenesulfonyl, C₆-C₁₄aryl-lower alkanesulfonyl or lower alkanesulfonyl.

N-Mono- or N,N-disubstituted aminosulfonyl is especially aminosulfonyl N-monosubstituted or N,N-disubstituted by lower alkyl, C₆-C₁₄aryl or C₆-C₁₄aryl-lower alkyl.

C₆-C₁₄Aryl is an aryl radical with 6 to 14 carbon atoms in the ring system, such as phenyl, naphthyl, fluorenyl, or indenyl, which is unsubstituted or is substituted especially by halogen, such as fluorine, chlorine, bromine, or iodine, phenyl or naphthyl, hydroxy, lower alkoxy, phenyl-lower alkoxy, phenyloxy, lower alkanoyloxy, benzoyloxy, amino, lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, sulfo, lower alkanesulfonyl, lower alkoxysulfonyl, aminosulfonyl, N-lower alkylaminosulfonyl, or N,N-di-lower alkylaminosulfonyl.

The indices n and m are in each case preferably 1, 2 or especially 0. In general, compounds of formula I in which n and m are in each case 0 (zero) are especially preferred.

An aliphatic carbohydrate radical R₃, R₄, R₈ or R₁₀ with up to 29 carbon atoms, which is substituted by acyclic substituents and preferably has a maximum of 18, especially a maximum of 12, and as a rule not more than 7 carbon atoms, may be saturated or unsaturated and is especially an unsubstituted or a straight-chain or branched lower alkyl, lower alkenyl, lower alkadienyl, or lower alkynyl radical substituted by acyclic substituents. Lower alkyl is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, and also n-

pentyl, isopentyl, n-hexyl, isohexyl and n-heptyl; lower alkenyl is, for example, allyl, propenyl, isopropenyl, 2- or 3-methallyl and 2- or 3-butenyl; lower alkadienyl is, for example, 1-penta-2,4-dienyl; lower alkinyl is, for example, propargyl or 2-butylnyl. In corresponding unsaturated radicals, the double bond is especially located in a position higher than the α -position in relation to the free valency. Substituents are especially the acyl radicals defined hereinbelow as substituents of R^0 , preferably free or esterified carboxy, such as carboxy or lower alkoxy-carbonyl, cyano or di-lower alkylamino.

A carbocyclic or carbocyclic-aliphatic radical R_3 , R_4 , R_8 or R_{10} with up to 29 carbon atoms in each case is especially an aromatic, a cycloaliphatic, a cycloaliphatic-aliphatic, or an aromatic-aliphatic radical which is either present in unsubstituted form or substituted by radicals referred to hereinbelow as substituents of R^0 . An aromatic radical (aryl radical) R_3 or R_4 is most especially a phenyl, also a naphthyl, such as 1- or 2-naphthyl, a biphenylyl, such as especially 4-biphenylyl, and also an anthryl, fluorenyl and azulenylyl, as well as their aromatic analogues with one or more saturated rings, which is either present in unsubstituted form or substituted by radicals referred to hereinbelow as substituents of R^0 . Preferred aromatic-aliphatic radicals are aryl-lower alkyl- and aryl-lower alkenyl radicals, e.g. phenyl-lower alkyl or phenyl-lower alkenyl with a terminal phenyl radical, such as for example benzyl, phenethyl, 1-, 2-, or 3-phenylpropyl, diphenylmethyl (benzhydryl), trityl, and cinnamyl, and also 1- or 2-naphthylmethyl. Of aryl radicals carrying acyclic radicals, such as lower alkyl, special mention is made of o-, m- and p-tolyl and xylyl radicals with variously situated methyl radicals.

A cycloaliphatic radical R_3 , R_4 , R_8 or R_{10} with up to 29 carbon atoms is especially a substituted or preferably unsubstituted mono-, bi-, or polycyclic cycloalkyl-, cycloalkenyl-, or cycloalkadienyl radical. Preference is for radicals with a maximum of 14, especially 12, ring-carbon atoms and 3- to 8-, preferably 5- to 7-, and most especially 6-member rings which can also carry one or more, for example two, aliphatic hydrocarbon radicals, for example those named above, especially the lower alkyl radicals, or other cycloaliphatic radicals as substituents. Preferred substituents are the acyclic substituents named hereinbelow for R^0 .

A cycloaliphatic-aliphatic radical R_3 , R_4 , R_8 or R_{10} with up to 29 carbon atoms is a radical in which an acyclic radical, especially one with a maximum of 7, preferably a maximum of 4 carbon atoms, such as especially methyl, ethyl, and vinyl, carries one or more cycloaliphatic radicals as defined hereinabove. Special mention is made of cycloalkyl-lower alkyl radicals, as well as their analogues which are unsaturated in the ring and/or in the chain, but are non-aromatic, and which

carry the ring at the terminal carbon atom of the chain. Preferred substituents are the acyclic substituents named herein below for R°.

Heterocyclic radicals R₃, R₄, R₈ or R₁₀ with up to 20 carbon atoms each and up to 9 heteroatoms each are especially monocyclic, but also bi- or polycyclic, aza-, thia-, oxa-, thiaza-, oxaza-, diaza-, triaza-, or tetrazacyclic radicals of an aromatic character, as well as corresponding heterocyclic radicals of this type which are partly or most especially wholly saturated, these radicals - if need be - possibly carrying further acyclic, carbocyclic, or heterocyclic radicals and/or possibly mono-, di-, or polysubstituted by functional groups, preferably those named hereinabove as substituents of aliphatic hydrocarbon radicals. Most especially they are unsubstituted or substituted monocyclic radicals with a nitrogen, oxygen, or sulfur atom, such as 2-aziridinyl, and especially aromatic radicals of this type, such as pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3-, or 4-pyridyl, and also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl; analogous bicyclic radicals with an oxygen, sulfur, or nitrogen atom are, for example, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, or benzothienyl, typically 2- or 3-benzothienyl; preferred monocyclic and bicyclic radicals with several heteroatoms are, for example, imidazolyl, typically 2- or 4-imidazolyl, pyrimidinyl, typically 2- or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, or thiazolyl, typically 2-thiazolyl, and benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, or quinazolyl, typically 2-quinazolyl. Appropriate partially or, especially, completely saturated analogous radicals may also be considered, such as 2-tetrahydrofuryl, 2- or 3-pyrrolidinyl, 2-, 3-, or 4-piperidyl, and also 2- or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl and N-mono- or N,N'-bis-lower alkyl-2-piperazinyl radicals. These radicals may also carry one or more acyclic, carbocyclic, or heterocyclic radicals, especially those mentioned hereinabove. The free valency of the heterocyclic radicals R₃ or R₄ must emanate from one of their carbon atoms. Heterocyclyl may be unsubstituted or substituted by one or more, preferably one or two, of the substituents named hereinbelow for R°.

Heterocyclic-aliphatic radicals R₃, R₄, R₈ or R₁₀ especially lower alkyl radicals, especially with a maximum of 7, preferably a maximum of 4 carbon atoms, for example those named hereinabove, which carry one, two, or more heterocyclic radicals, for example those named in the preceding paragraph, the heterocyclic ring possibly being linked to the aliphatic chain also by one of its nitrogen atoms. A preferred heterocyclic-aliphatic radical R₁ is, for example, imidazol-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, piperazin-1-ylmethyl, 2-(morpholin-4-yl)ethyl and also

pyrid-3-ylmethyl. Heterocyclyl may be unsubstituted or substituted by one or more, preferably one or two, of the substituents named hereinbelow for R° .

A heteroaliphatic radical R_3 , R_4 , R_8 or R_{10} with up to 20 carbon atoms each and up to 10 heteroatoms each is an aliphatic radical which, instead of one, two, or more carbon atoms, contains identical or different heteroatoms, such as especially oxygen, sulfur, and nitrogen. An especially preferred arrangement of a heteroaliphatic radical R_1 takes the form of oxa-alkyl radicals in which one or more carbon atoms are replaced in a preferably linear alkyl by oxygen atoms preferably separated from one another by several (especially 2) carbon atoms so that they form a repeating group, if need be multi-repeating group $(O-CH_2-CH_2-)_q$, wherein $q = 1$ to 7 .

Especially preferred as R_3 , R_4 , R_8 or R_{10} , apart from acyl, is lower alkyl, particularly methyl or ethyl; lower alkoxy-carbonyl-lower alkyl, especially methoxycarbonylmethyl or 2-(tert-butoxycarbonyl)ethyl; carboxy-lower alkyl, especially carboxymethyl or 2-carboxyethyl; or cyano-lower alkyl, especially 2-cyanoethyl.

An acyl radical R_3 , R_4 , R_6 , R_7 , R_8 , R_9 , or R_{10} with up to 30 carbon atoms derives from a carboxylic acid, functionally modified if need be, an organic sulfonic acid, or a phosphoric acid, such as pyro- or orthophosphoric acid, esterified if need be.

An acyl designated Ac^1 and derived from a carboxylic acid, functionally modified if need be, is especially one of the subformula $Y-C(=W)-$, wherein W is oxygen, sulfur, or imino and Y is hydrogen, hydrocarbyl R° with up to 29 carbon atoms, hydrocarbyloxy $R^\circ-O-$, an amino group or a substituted amino group, especially one of the formula $R^\circ HN-$ or $R^\circ R^\circ N-$ (wherein the R° radicals may be identical or different from one another).

The hydrocarbyl (hydrocarbon radical) R° is an acyclic (aliphatic), carbocyclic, or carbocyclic-acyclic hydrocarbon radical, with up to 29 carbon atoms each, especially up to 18, and preferably up to 12 carbon atoms, and is saturated or unsaturated, unsubstituted or substituted. Instead of one, two, or more carbon atoms, it may contain identical or different heteroatoms, such as especially oxygen, sulfur, and nitrogen in the acyclic and/or cyclic part; in the latter case, it is described as a heterocyclic radical (heterocyclyl radical) or a heterocyclic-acyclic radical.

Unsaturated radicals are those, which contain one or more, especially conjugated and/or isolated, multiple bonds (double or triple bonds). The term cyclic radicals includes also aromatic

and non-aromatic radicals with conjugated double bonds, for example those wherein at least one 6-member carbocyclic or a 5- to 8-member heterocyclic ring contains the maximum number of non-cumulative double bonds. Carbocyclic radicals, wherein at least one ring is present as a 6-member aromatic ring (i.e. a benzene ring), are defined as aryl radicals.

An acyclic unsubstituted hydrocarbon radical R° is especially a straight-chained or branched lower alkyl-, lower alkenyl-, lower alkadienyl-, or lower alkynyl radical. Lower alkyl R° is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, and also n-pentyl, isopentyl, n-hexyl, isohexyl and n-heptyl; lower alkenyl is, for example, allyl, propenyl, isopropenyl, 2- or 3-methallyl and 2- or 3-butenyl; lower alkadienyl is, for example, 1-penta-2,4-dienyl; lower alkynyl is, for example, propargyl or 2-butylnyl. In corresponding unsaturated radicals, the double bond is especially located in a position higher than the α -position in relation to the free valency.

A carbocyclic hydrocarbon radical R° is especially a mono-, bi-, or polycyclic cycloalkyl-, cycloalkenyl-, or cycloalkadienyl radical, or a corresponding aryl radical. Preference is for radicals with a maximum of 14, especially 12, ring-carbon atoms and 3- to 8-, preferably 5- to 7-, and most especially 6-member rings which can also carry one or more, for example two, acyclic radicals, for example those named above, especially the lower alkyl radicals, or other carbocyclic radicals. Carbocyclic-acyclic radicals are those in which an acyclic radical, especially one with a maximum of 7, preferably a maximum of 4 carbon atoms, such as especially methyl, ethyl and vinyl, carries one or more carbocyclic, if need be aromatic radicals of the above definition. Special mention is made of cycloalkyl-lower and aryl-lower alkyl radicals, as well as their analogues which are unsaturated in the ring and/or chain, and which carry the ring at the terminal carbon atom of the chain.

Cycloalkyl R° has most especially from 3 up to and including 10 carbon atoms and is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, as well as bicyclo[2,2,2]octyl, 2-bicyclo[2,2,1]heptyl, and adamantyl, which may also be substituted by 1, 2, or more, for example lower, alkyl radicals, especially methyl radicals; cycloalkenyl is for example one of the monocyclic cycloalkyl radicals already named which carries a double bond in the 1-, 2-, or 3 position. Cycloalkyl-lower alkyl or -lower alkenyl is for example a -methyl, -1- or -2-ethyl, -1- or -2-vinyl, -1-, -2-, or -3-propyl or -allyl substituted by one of the above-named cycloalkyl radicals, those substituted at the end of the linear chain being preferred.

An aryl radical R^0 is most especially a phenyl, also a naphthyl, such as 1- or 2-naphthyl, a biphenyl, such as especially 4-biphenyl, and also an anthryl, fluorenyl and azulenyl, as well as their aromatic analogues with one or more saturated rings. Preferred aryl-lower alkyl and -lower alkenyl radicals are, for example, phenyl-lower alkyl or phenyl-lower alkenyl with a terminal phenyl radical, such as for example benzyl, phenethyl, 1-, 2-, or 3-phenylpropyl, diphenylmethyl (benzhydryl), trityl, and cinnamyl, and also 1- or 2-naphthylmethyl. Aryl may be unsubstituted or substituted.

Heterocyclic radicals, including heterocyclic-acyclic radicals, are especially monocyclic, but also bi- or polycyclic, aza-, thia-, oxa-, thiaza-, oxaza-, diaza-, triaza-, or tetrazacyclic radicals of an aromatic character, as well as corresponding heterocyclic radicals of this type which are partly or most especially wholly saturated; if need be, for example as in the case of the above-mentioned carbocyclic or aryl radicals, these radicals may carry further acyclic, carbocyclic, or heterocyclic radicals and/or may be mono-, di-, or polysubstituted by functional groups. The acyclic part in heterocyclic-acyclic radicals has for example the meaning indicated for the corresponding carbocyclic-acyclic radicals. Most especially they are unsubstituted or substituted monocyclic radicals with a nitrogen, oxygen, or sulfur atom, such as 2-aziridinyl, and especially aromatic radicals of this type, such as pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3-, or 4-pyridyl, and also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl; analogous bicyclic radicals with an oxygen, sulfur, or nitrogen atom are, for example, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, or benzothienyl, typically 2- or 3-benzothienyl; preferred monocyclic and bicyclic radicals with several heteroatoms are, for example, imidazolyl, typically 2-imidazolyl, pyrimidinyl, typically 2- or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, or thiazolyl, typically 2-thiazolyl, and benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, or quinazolyl, typically 2-quinazolyl. Appropriate partially or, especially, completely saturated analogous radicals may also be considered, such as 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 3-pyrrolidyl, 2-, 3-, or 4-piperidyl, and also 2- or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl, and N,N'-bis-lower alkyl-2-piperazinyl radicals. These radicals may also carry one or more acyclic, carbocyclic, or heterocyclic radicals, especially those mentioned hereinabove. Heterocyclic-acyclic radicals are especially derived from acyclic radicals with a maximum of 7, preferably a maximum of 4 carbon atoms, for example those named hereinabove, and may carry one, two, or more heterocyclic radicals, for example those named hereinabove, the ring possibly being linked to the aliphatic chain also by one of its nitrogen -

atoms.

As already mentioned, a hydrocarbyl (including a heterocyclyl) may be substituted by one, two, or more identical or different substituents (functional groups); one or more of the following substituents may be considered: lower alkyl; free, etherified and esterified hydroxyl groups; carboxy groups and esterified carboxy groups; mercapto- and lower alkylthio- and, if need be, substituted phenylthio groups; halogen atoms, typically chlorine and fluorine, but also bromine and iodine; *halogen-lower alkyl groups*; oxo groups which are present in the form of formyl (i.e. aldehydo) and keto groups, also as corresponding acetals or ketals; azido groups; nitro groups; cyano groups; primary, secondary and preferably tertiary amino groups, amino-lower alkyl, mono- or disubstituted amino-lower alkyl, primary or secondary amino groups protected by conventional protecting groups (especially lower alkoxycarbonyl, typically tert-butoxycarbonyl) lower alkylenedioxy, and also free or functionally modified sulfo groups, typically sulfamoyl or sulfo groups present in free form or as salts. The hydrocarbyl radical may also carry carbamoyl, ureido, or guanidino groups, which are free or which carry one or two substituents, and cyano groups. The above use of the word "groups" is taken to imply also an individual group.

Halogen-lower alkyl contains preferably 1 to 3 halogen atoms; preferred is trifluoromethyl or chloromethyl.

An etherified hydroxyl group present in the hydrocarbyl as substituent is, for example, a lower alkoxy group, typically the methoxy-, ethoxy-, propoxy-, isopropoxy-, butoxy-, and tert-butoxy group, which may also be substituted, especially by (i) heterocyclyl, whereby heterocyclyl can have preferably 4 to 12 ring atoms, may be unsaturated, or partially or wholly saturated, is mono- or bicyclic, and may contain up to three heteroatoms selected from nitrogen, oxygen, and sulfur, and is most especially pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, and also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2- or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2- or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl; and also (ii) by halogen atoms, for example

mono-, di-, or polysubstituted especially in the 2-position, as in the 2,2,2-trichloroethoxy, 2-chloroethoxy, or 2-iodoethoxy radical, or (iii) by hydroxy or (iv) lower alkoxy radicals, each preferably monosubstituted, especially in the 2-position, as in the 2-methoxyethoxy radical. Such etherified hydroxyl groups are also unsubstituted or substituted phenoxy radicals and phenyl-lower alkoxy radicals, such as especially benzyloxy, benzhydryloxy, and triphenylmethoxy (trityloxy), as well as heterocyclyloxy radicals, wherein heterocyclyl can have preferably 4 to 12 ring atoms, may be unsaturated, or partially or wholly saturated, is mono- or bicyclic, and may contain up to three heteroatoms selected from nitrogen, oxygen, and sulfur, and is most especially pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, and also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2- or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolinyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2- or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl; such as especially 2- or 4-tetrahydropyranyloxy.

Etherified hydroxyl groups in this context are taken to include silylated hydroxyl groups, typically for example tri-lower alkylsilyloxy, typically trimethylsilyloxy and dimethyl-tert-butylsilyloxy, or phenyldi-lower alkylsilyloxy and lower alkyl-diphenylsilyloxy.

An esterified hydroxyl group present in the hydrocarbyl as a substituent is, for example, lower -alkanoyloxy.

A carboxyl group present in the hydrocarbyl as a substituent is one in which the hydrogen atom is replaced by one of the hydrocarbyl radicals characterised hereinabove, preferably a lower alkyl- or phenyl-lower alkyl radical; an example of an esterified carboxyl group is lower alkoxycarbonyl or phenyl-lower alkoxycarbonyl substituted if need be in the phenyl part, especially the methoxy, ethoxy, tert-butoxy, and benzyloxycarbonyl group, as well as a lactonised carboxyl group.

A primary amino group $-NH_2$ as substituent of the hydrocarbyls may also be present in a form protected by a conventional protecting group. A secondary amino group carries, instead of one

of the two hydrogen atoms, a hydrocarbonyl radical, preferably an unsubstituted one, typically one of the above-named, especially lower alkyl, and may also be present in protected form.

A tertiary amino group present in the hydrocarbonyl as substituent carries 2 different or, preferably, identical hydrocarbonyl radicals (including the heterocyclic radicals), such as the unsubstituted hydrocarbonyl radicals characterised hereinabove, especially lower alkyl.

A preferred amino group is one with the formula $R_{11}(R_{12})N-$, wherein R_{11} and R_{12} are independently in each case hydrogen, unsubstituted acyclic C_1 - C_7 -hydrocarbonyl (such as especially C_1 - C_4 alkyl or C_2 - C_4 alkenyl) or monocyclic aryl, aralkyl, or aralkenyl, substituted if necessary by C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, halogen, and/or nitro, and having a maximum of 10 carbon atoms, where the carbon-containing radicals may be interlinked through a carbon-carbon bond or an oxygen atom, a sulfur atom, or a nitrogen atom substituted if necessary by hydrocarbonyl. In such a case, they form a nitrogen-containing heterocyclic ring with the nitrogen atom of the amino group. The following are examples of especially preferred disubstituted amino groups: di-lower alkylamino, typically dimethylamino or diethylamino, pyrrolidino, imidazol-1-yl, piperidino, piperazino, 4-lower alkylpiperazino, morpholino, thiomorpholino and piperazino or 4-methylpiperazino, as well as diphenylamino and dibenzylamino substituted if need be, especially in the phenyl part, for example by lower-alkyl, lower-alkoxy, halogen, and/or nitro; of the protected groups, especially lower alkoxycarbonylamino, typically tert-butoxycarbonylamino, phenyl-lower alkoxycarbonylamino, typically 4-methoxybenzyloxycarbonylamino, and 9-fluorenylmethoxycarbonylamino.

Amino-lower alkyl is most especially substituted in the 1-position of the lower alkyl chain by amino and is especially aminomethyl.

Mono- or disubstituted amino-lower alkyl is amino-lower alkyl substituted by one or two radicals, wherein amino-lower alkyl is most especially substituted by amino in the 1-position of the lower alkyl chain and is especially aminomethyl; the amino substituents here are preferably (if 2 substituents are present in the respective amino group independently of one another) from the group comprising lower alkyl, such as especially methyl, ethyl or n-propyl, hydroxy-lower alkyl, typically 2-hydroxyethyl, C_3 - C_8 cycloalkyl, especially cyclohexyl, amino-lower alkyl, typically 3-aminopropyl or 4-aminobutyl, N-mono- or N,N-di(lower alkyl)-amino-lower alkyl, typically 3-(N,N-dimethylamino)propyl, amino, N-mono- or N,N-di-lower alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino.

Disubstituted amino-lower alkyl is also a 5 or 6-membered, saturated or unsaturated heterocyclyl bonded to lower alkyl via a nitrogen atom (preferably in the 1-position) and having 0 to 2, especially 0 or 1, other heteroatoms selected from oxygen, nitrogen, and sulfur, which is unsubstituted or substituted, especially by one or two radicals from the group comprising lower alkyl, typically methyl, and also oxo. Preferred here is pyrrolidino (1-pyrrolidinyl), piperidino (1-piperidinyl), piperazino (1-piperazinyl), 4-lower alkylpiperazino, typically 4-methylpiperazino, imidazolino (1-imidazolyl), morpholino (4-morpholinyl), or also thiomorpholino, S-oxo-thiomorpholino, or S,S-dioxothiomorpholino.

Lower alkylenedioxy is especially methylenedioxy.

A carbamoyl group carrying one or two substituents is especially aminocarbonyl (carbamoyl) which is substituted by one or two radicals at the nitrogen; the amino substituents here are preferably (if 2 substituents are present in the respective amino group independently of one another) from the group comprising lower alkyl, such as especially methyl, ethyl or n-propyl, hydroxy-lower alkyl, typically 2-hydroxyethyl, C₃-C₈cycloalkyl, especially cyclohexyl, amino-lower alkyl, typically 3-aminopropyl or 4-aminobutyl, N-mono- or N,N-di(lower alkyl)-amino-lower alkyl, typically 3-(N,N-dimethylamino)propyl, amino, N-mono- or N,N-di-lower alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino; disubstituted amino in aminocarbamoyl is also a 5 or 6-membered, saturated or unsaturated heterocyclyl with a bonding nitrogen atom and 0 to 2, especially 0 or 1, other heteroatoms selected from oxygen, nitrogen, and sulfur, which is unsubstituted or substituted, especially by one or two radicals from the group comprising lower alkyl, typically methyl, and also oxo. Preferred here is pyrrolidino (1-pyrrolidinyl), piperidino (1-piperidinyl), piperazino (1-piperazinyl), 4-lower alkylpiperazino, typically 4-methylpiperazino, imidazolino (1-imidazolyl), morpholino (4-morpholinyl), or also thiomorpholino, S-oxo-thiomorpholino, or S,S-dioxothiomorpholino.

An acyl derived from an organic sulfonic acid, which is designated Ac², is especially one with the subformula R^o-SO₂-, wherein R^o is a hydrocarbonyl as defined above in the general and specific meanings, the latter also being generally preferred here. Especially preferred is lower alkylphenylsulfonyl, especially 4-toluenesulfonyl.

An acyl derived from a phosphoric acid, esterified if necessary, which is designated Ac³, is especially one with the subformula R^oO(R^oO)P(=O)-, wherein the radicals R^o are, independently

of one another, as defined in the general and specific meanings indicated above.

Reduced data on substituents given hereinbefore and hereinafter are considered to be preferences.

Preferred compounds according to the invention are, for example, those wherein R^0 has the following preferred meanings: lower alkyl, especially methyl or ethyl, amino-lower alkyl, wherein the amino group is unprotected or is protected by a conventional amino protecting group - especially by lower alkoxy carbonyl, typically tert-lower alkoxy carbonyl, for example tert-butoxy carbonyl - e.g. aminomethyl, R,S-, R- or preferably S-1-aminoethyl, tert-butoxycarbonylaminomethyl or R,S-, R-, or preferably S-1-(tert-butoxycarbonylamino)ethyl, carboxy-lower alkyl, typically 2-carboxyethyl, lower alkoxy carbonyl-lower alkyl, typically 2-(tert-butoxycarbonyl)ethyl, cyano-lower alkyl, typically 2-cyanoethyl, tetrahydropyranyloxy-lower alkyl, typically 4-(tetrahydropyranyl)-oxymethyl, morpholino-lower alkyl, typically 2-(morpholino)ethyl, phenyl, lower alkylphenyl, typically 4-methylphenyl, lower alkoxyphenyl, typically 4-methoxyphenyl, imidazolyl-lower alkoxyphenyl, typically 4-[2-(imidazol-1-yl)ethyl]oxyphenyl, carboxyphenyl, typically 4-carboxyphenyl, lower alkoxy carbonylphenyl, typically 4-ethoxycarbonylphenyl or 4-methoxyphenyl, halogen-lower alkylphenyl, typically 4-chloromethylphenyl, pyrrolidinophenyl, typically 4-pyrrolidinophenyl, imidazol-1-ylphenyl, typically 4-(imidazol-1-yl)phenyl, piperazinophenyl, typically 4-piperazinophenyl, (4-lower alkylpiperazino)phenyl, typically 4-(4-methylpiperazino)phenyl, morpholinophenyl, typically 4-morpholinophenyl, pyrrolidino-lower alkylphenyl, typically 4-pyrrolidinomethylphenyl, imidazol-1-yl-lower alkylphenyl, typically 4-(imidazol-1-ylmethyl)phenyl, piperazino-lower alkylphenyl, typically 4-piperazinomethylphenyl, (4-lower alkylpiperazinomethyl)-phenyl, typically 4-(4-methylpiperazinomethyl)phenyl, morpholino-lower alkylphenyl, typically 4-morpholinomethylphenyl, piperazinocarbonylphenyl, typically 4-piperazinocarbonylphenyl, or (4-lower alkyl-piperazino)phenyl, typically 4-(4-methylpiperazino)phenyl.

Preferred acyl radicals Ac^1 are acyl radicals of a carboxylic acid which are characterised by the subformula R^0-CO- , wherein R^0 has one of the above general and preferred meanings of the hydrocarbyl radical R^0 . Especially preferred radicals R^0 here are lower alkyl, especially methyl or ethyl, amino-lower alkyl, wherein the amino group is unprotected or protected by a conventional amino protecting group, especially by lower alkoxy carbonyl, typically tert-lower alkoxy carbonyl, for example tert-butoxycarbonyl, e.g. aminomethyl, R,S-, R-, or preferably S-1-aminoethyl, tert-butoxycarbonylaminomethyl or R,S-, R-, or preferably S-1-(tert-butoxycarbonylamino)ethyl,

carboxy-lower alkyl, typically 2-carboxyethyl, lower alkoxycarbonyl-lower alkyl, typically 2-(tert-butoxycarbonyl)ethyl, tetrahydropyranyloxy-lower alkyl, typically 4-(tetrahydropyranyl)oxymethyl, phenyl, imidazolyl-lower alkoxyphenyl, typically 4-[2-(imidazol-1-yl)ethyl]oxyphenyl, carboxyphenyl, typically 4-carboxyphenyl, lower alkoxycarbonylphenyl, typically 4-ethoxycarbonylphenyl, halogen-lower alkylphenyl, typically 4-chloromethylphenyl, imidazol-1-ylphenyl, typically 4-(imidazolyl-1-yl)phenyl, pyrrolidino-lower alkylphenyl, typically 4-pyrrolidinomethylphenyl, piperazino-lower alkylphenyl, typically 4-piperazinomethylphenyl, (4-lower alkylpiperazinomethyl)phenyl, typically 4-(4-methylpiperazinomethyl)phenyl, morpholino-lower alkylphenyl, typically 4-morpholinomethylphenyl, piperazinocarbonylphenyl, typically 4-piperazinocarbonylphenyl, or (4-lower alkylpiperazino)phenyl, typically 4-(4-methylpiperazino)phenyl.

A further preferred Acyl Ac¹ is derived from monoesters of carbonic acid and is characterised by the subformula R^o-O-CO-. The lower alkyl radicals, especially tert-butyl, are especially preferred hydrocarbyl radicals R^o in these derivatives.

Another preferred Acyl Ac¹ is derived from amides of carbonic acid (or also thiocarbonic acid) and is characterised by the formula R^oHN-C(=W)- or R^oR^oN-C(=W)-, wherein the radicals R^o are, independently of one another, as defined above and W is sulfur and especially oxygen. In particular, compounds are preferred wherein Ac¹ is a radical of formula R^oHN-C(=W)-, wherein W is oxygen and R^o has one of the following preferred meanings: morpholino-lower alkyl, typically 2-morpholinoethyl, phenyl, lower alkoxyphenyl, typically 4-methoxyphenyl or 4-ethoxyphenyl, carboxyphenyl, typically 4-carboxyphenyl, or lower alkoxycarbonylphenyl, typically 4-ethoxycarbonylphenyl.

A preferred acyl Ac² of subformula R^o-SO₂-, wherein R^o is a hydrocarbyl as defined in the above general and specific meanings, is lower alkylphenylsulfonyl, typically 4-toluenesulfonyl.

If p is 0, the nitrogen atom bonding R₃ is uncharged. If p is 1, then R₄ must also be present, and the nitrogen atom bonding R₃ and R₄ (quaternary nitrogen) is then positively charged.

The definitions for an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms each, or for a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms each and up to 9 heteroatoms each, or acyl with up to 30 carbon atoms each, preferably match the definitions given for the corresponding radicals R₃ and R₄. Especially preferred is R₅ lower -

alkyl, especially methyl, or most especially hydrogen.

Z is especially lower alkyl, most especially methyl or hydrogen.

If the two bonds indicated by wavy lines are missing in ring A, then no double bonds (tetra-hydrogenated derivatives) are present between the carbon atoms characterised in formula I by the numbers 1, 2, 3, and 4, but only single bonds, whereas ring B is aromatic (double bonds between the carbon atoms characterised in formula I by 8 and 9 and those characterised by 10 and 11). If the two bonds indicated by wavy lines are missing in ring B, then no double bonds (tetra-hydrogenated derivatives) are present between the carbon atoms characterised in formula I by the numbers 8, 9, 10, and 11, but only single bonds, whereas ring A is aromatic (double bonds between the carbon atoms characterised in formula I by 1 and 2 and those characterised by 3 and 4). If the total of four bonds indicated by wavy lines are missing in rings A and B, and are replaced by a total of 8 hydrogen atoms, then no double bonds (octa-hydrogenated derivatives) are present between the carbon atoms numbered 1, 2, 3, 4, 8, 9, 10, and 11 in formula I, but only single bonds.

By their nature, the compounds of the invention may also be present in the form of pharmaceutically, i.e. physiologically, acceptable salts, provided they contain salt-forming groups. For isolation and purification, pharmaceutically unacceptable salts may also be used. For therapeutic use, only pharmaceutically acceptable salts are used, and these salts are preferred.

Thus, compounds of formula I having free acid groups, for example a free sulfo, phosphoryl or carboxyl group, may exist as a salt, preferably as a physiologically acceptable salt with a salt-forming basic component. These may be primarily metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines, especially tertiary monoamines and heterocyclic bases, for example triethylamine, tri-(2-hydroxyethyl)-amine, N-ethylpiperidine or N,N'-dimethylpiperazine.

Compounds of the invention having a basic character may also exist as addition salts, especially as acid addition salts with inorganic and organic acids, but also as quaternary salts. Thus, for example, compounds which have a basic group, such as an amino group, as a substituent may form acid addition salts with common acids. Suitable acids are, for example, hydrohalic acids,

e.g. hydrochloric and hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid or perchloric acid, or aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, fumaric, maleic, hydroxymaleic, oxalic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, anthranilic, p-hydroxybenzoic, salicylic, p-aminosalicylic acid, pamoic acid, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenedisulfonic, halobenzenesulfonic, toluenesulfonic, naphthalenesulfonic acids or sulfanilic acid, and also methionine, tryptophan, lysine or arginine, as well as ascorbic acid.

In view of the close relationship between the compounds (especially of formula I) in free form and in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, and of their solvates, any reference hereinbefore and hereinafter to the free compounds is to be understood as referring also to the corresponding salts, and the solvates thereof, for example hydrates, as appropriate and expedient.

The compounds of formula A, B, C, D, I, II, III, IV, V or VI especially those wherein R₅ is hydrogen, possess valuable pharmacological properties.

In the case of the groups of radicals or compounds mentioned hereinbefore and hereinafter, general definitions may, insofar as appropriate and expedient, be replaced by the more specific definitions stated hereinbefore and hereinafter.

Preference is given to a compounds of formula I, II, III, IV, V, VI wherein

R₁ and R₂ independently of each other are lower alkyl, lower alkyl substituted by halogen, C₆-C₁₄aryl, hydroxy, lower alkoxy, phenyl-lower alkoxy, phenyloxy, lower alkanoyloxy, benzoyloxy, amino, lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, sulfo, lower alkanesulfonyl, lower alkoxysulfonyl, aminosulfonyl, N-lower alkylaminosulfonyl or N,N-di-lower alkylaminosulfonyl; halogen; lower alkoxy; C₆-C₁₄aryloxy; C₆-C₁₄aryl-lower alkoxy; lower alkanoyloxy; C₆-C₁₄arylcarbonyloxy; amino monosubstituted or disubstituted by lower alkyl, C₆-C₁₄aryl, C₆-C₁₄aryl-lower alkyl, lower alkanoyl or C₆-C₁₂arylcarbonyl; cyano; nitro; mercapto; lower alkylthio; C₆-C₁₄arylthio; C₆-C₁₄aryl-lower alkylthio; lower alkanoylthio; C₆-C₁₄aryl-lower alkanoylthio; carboxy; lower alkoxycarbonyl, C₆-C₁₄aryl-lower alkoxycarbonyl; C₆-C₁₄aryloxycarbonyl; carbamoyl; carbamoyl N-mono- or N,N-disubstituted by lower alkyl, C₆-

C₁₄aryl or C₆-C₁₄aryl-lower alkyl; sulfo; C₆-C₁₄arylsulfonyl; C₆-C₁₄aryl-lower alkanesulfonyl; lower alkanesulfonyl; or aminosulfonyl N-mono- or N,N-disubstituted by lower alkyl, C₆-C₁₄aryl or C₆-C₁₄aryl-lower alkyl, wherein C₆-C₁₄aryl is an aryl radical with 6 to 12 carbon atoms in the ring system, which may be unsubstituted or substituted by halogen, phenyl or naphthyl, hydroxy, lower alkoxy, phenyl-lower alkoxy, phenyloxy, lower alkanoyloxy, benzoyloxy, amino, lower alkylamino, lower alkanoylamino, phenyl-lower alkylamino, N,N-di-lower alkylamino, N,N-di-(phenyl-lower alkyl)amino, cyano, mercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, sulfo, lower alkanesulfonyl, lower alkoxysulfonyl, aminosulfonyl, N-lower alkylaminosulfonyl or N,N-di-lower alkylamino-sulfonyl;

n and m are independently of each other 0 or 1 or 2, preferably 0;

R₃, R₄, R₈, R₁₀ are independently of each other hydrogen, lower alkyl, lower alkenyl or lower alkadienyl, which are each unsubstituted or monosubstituted or polysubstituted, preferably monosubstituted or disubstituted by a substituent independently selected from lower alkyl; hydroxy; lower alkoxy, which may be unsubstituted or mono-, di-, or trisubstituted by (i) heterocyclyl with 4 to 12 ring atoms, which may be unsaturated, wholly saturated, or partly saturated, is monocyclic or bicyclic and may contain up to three heteroatoms selected from nitrogen, oxygen and sulfur, and is most especially pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, or in a broader sense also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2- or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolinyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2- or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl, (ii) by halogen, (iii) by hydroxy or (iv) by lower alkoxy; phenoxy; phenyl-lower alkoxy; heterocyclyloxy, wherein heterocyclyl is pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, or in a broader sense also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-

imidazolyl, pyrimidinyl, typically 2-or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2-or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl, such as especially 2- or 4-tetrahydropyranyloxy; lower alkanoyloxy; carboxy; lower alkoxycarbonyl; phenyl-lower alkoxycarbonyl; mercapto; lower alkylthio; phenylthio; halogen; halogen-lower alkyl; oxo (except in the 1-position, because otherwise acyl); azido; nitro; cyano; amino; mono-lower alkylamino; di-lower alkylamino; pyrrolidino; imidazol-1-yl; piperidino; piperazino; 4-lower alkylpiperazino; morpholino; thiomorpholino; diphenylamino or dibenzylamino unsubstituted or substituted in the phenyl part by lower alkyl, lower alkoxy, halogen and/or nitro; lower alkoxycarbonylamino; phenyl-lower alkoxycarbonylamino unsubstituted or substituted in the phenyl part by lower alkyl or lower alkoxy; fluorenylmethoxycarbonylamino; amino-lower alkyl; monosubstituted or disubstituted amino-lower alkyl, wherein the amino substituent is selected from lower alkyl, hydroxy-lower alkyl, C₃-C₈cycloalkyl, amino-lower alkyl, N-mono- or N,N-di(-lower alkyl)amino-lower alkyl, amino, N-mono- or N,N-di-lower alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino; pyrrolidino-lower alkyl; piperidino-lower alkyl; piperazino-lower alkyl; 4-lower alkylpiperazino-lower alkyl; imidazol-1-yl-lower alkyl; morpholino-lower alkyl; thiomorpholino-lower alkyl; S-oxo-thiomorpholino-lower alkyl; S,S-dioxothiomorpholino-lower alkyl; lower alkylendioxy; sulfamoyl; sulfo; carbamoyl; ureido; guanidino; cyano; aminocarbonyl (carbamoyl) and aminocarbonyloxy, which are substituted by one or two radicals on the nitrogen, wherein the amino substituents are selected independently of one another from the group comprising lower alkyl, hydroxy-lower alkyl, C₃-C₈cycloalkyl, amino-lower alkyl, N-mono- or N,N-di(-lower alkyl)amino-lower alkyl, amino, N-mono- or N,N-di-lower alkylamino and N-mono- or N,N-di-(hydroxy-lower alkyl)amino; pyrrolidinocarbonyl; piperidinocarbonyl; piperazinocarbonyl; 4-lower alkylpiperazinocarbonyl; imidazolinocarbonyl; morpholinocarbonyl; thiomorpholinocarbonyl; S-oxo-thiomorpholinocarbonyl; and S,S-dioxothiomorpholino;

phenyl, naphthyl, phenyl-lower alkyl or phenyl-lower alkenyl with a terminal phenyl radical, which is unsubstituted or monosubstituted or disubstituted by the radicals named above as substituents of lower alkyl, lower alkenyl or lower alkadienyl;

or heterocyclyl-lower alkyl, wherein heterocyclyl is pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, pyridyl, for example 2-, 3- or 4-pyridyl, or in a broader sense also thienyl, for example 2- or 3-thienyl, or furyl, for example 2-furyl, indolyl, typically 2- or 3-indolyl, quinolyl, typically 2- or 4-

quinolyl, isoquinolyl, typically 3- or 5-isoquinolyl, benzofuranyl, typically 2-benzofuranyl, chromenyl, typically 3-chromenyl, benzothienyl, typically 2- or 3-benzothienyl; imidazolyl, typically 1- or 2-imidazolyl, pyrimidinyl, typically 2- or 4-pyrimidinyl, oxazolyl, typically 2-oxazolyl, isoxazolyl, typically 3-isoxazolyl, thiazolyl, typically 2-thiazolyl, benzimidazolyl, typically 2-benzimidazolyl, benzoxazolyl, typically 2-benzoxazolyl, quinazolyl, typically 2-quinazolinyl, 2-tetrahydrofuryl, 4-tetrahydrofuryl, 2- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidyl, 1-, 2-, 3-, or 4-piperidyl, 1-, 2- or 3-morpholinyl, 2- or 3-thiomorpholinyl, 2-piperazinyl or N,N'-bis-lower alkyl-2-piperazinyl, which in each case are unsubstituted or monosubstituted or disubstituted by the radicals named above as substituents of lower alkyl, lower alkenyl, or lower alkadienyl;

or acyl of the subformula $Y-C(=W)-$, wherein W is oxygen and Y is hydrogen, R^0 , R^0-O- , R^0HN- , or R^0R^0N- (wherein the radicals R^0 may be the same or different),

or

acyl of the subformula R^0-SO_2- ,

whereby R_4 may also be absent for the compound of formula II;

or

R_4 is absent for compounds of formula II, hydrogen or CH_3 for compounds of formula I, and R_3 is acyl of the subformula $Y-C(=W)-$, wherein W is oxygen and Y is hydrogen, R^0 , R^0-O- , R^0HN- , or R^0R^0N- (wherein the radicals R^0 may be the same or different),

or

is acyl of the subformula R^0-SO_2- ,

wherein R^0 in the said radicals has the following meanings: substituted or unsubstituted lower alkyl, especially methyl or ethyl, amino-lower alkyl hydroxy-lower alkyl, wherein the amino group is unprotected or is protected by a conventional amino protecting group - especially by lower alkoxy-carbonyl, typically tert-lower alkoxy-carbonyl, for example tert-butoxy-carbonyl - e.g. aminomethyl, R,S-, R- or preferably S-1-aminoethyl, tert-butoxy-carbonylaminomethyl or R,S-, R-, or preferably S-1-(tert-butoxy-carbonylamino)ethyl, carboxy-lower alkyl, typically 2-carboxyethyl, lower alkoxy-carbonyl-lower alkyl, typically 2-(tert-butoxy-carbonyl)ethyl, cyano-lower alkyl, typically 2-cyanoethyl, tetrahydropyranyloxy-lower alkyl, typically 4-(tetrahydropyranyl)oxymethyl, morpholino-lower alkyl, typically 2-(morpholino)ethyl, phenyl, lower alkylphenyl, typically 4-methylphenyl, lower alkoxyphenyl, typically 4-methoxyphenyl, imidazolyl-lower alkoxyphenyl, typically 4-[2-(imidazol-1-yl)ethyl]oxyphenyl, carboxyphenyl, typically 4-carboxyphenyl, lower alkoxy-carbonylphenyl, typically 4-ethoxy-carbonylphenyl or 4-

methoxyphenyl, halogen-lower alkylphenyl, typically 4-chloromethylphenyl, pyrrolidinophenyl, typically 4-pyrrolidinophenyl, imidazol-1-ylphenyl, typically 4-(imidazolyl-1-yl)phenyl, piperazinophenyl, typically 4-piperazinophenyl, (4-lower alkylpiperazino)phenyl, typically 4-(4-methylpiperazino)phenyl, morpholinophenyl, typically 4-morpholinophenyl, pyrrolidino-lower alkylphenyl, typically 4-pyrrolidinomethylphenyl, imidazol-1-yl-lower alkylphenyl, typically 4-(imidazolyl-1-ylmethyl)phenyl, piperazino-lower alkylphenyl, typically 4-piperazinomethylphenyl, (4-lower alkylpiperazinomethyl)-phenyl, typically 4-(4-methylpiperazinomethyl)phenyl, morpholino-lower alkylphenyl, typically 4-morpholinomethylphenyl, piperazinocarbonylphenyl, typically 4-piperazinocarbonylphenyl, or (4-lower alkylpiperazino)phenyl, typically 4-(4-methylpiperazino)phenyl.

p is 0 if R₄ is absent, or is 1 if R₃ and R₄ are both present and in each case are one of the aforementioned radicals (for compounds of formula II);

R₅ is hydrogen or lower alkyl, especially hydrogen,

X stands for 2 hydrogen atoms, for O, or for 1 hydrogen atom and hydroxy; or for 1 hydrogen atom and lower alkoxy;

Z is hydrogen or especially lower alkyl, most especially methyl;

and for compounds for formula II, either the two bonds characterised by wavy lines are preferably absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or also the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present.

Particular preference is given to a compound of formula I wherein;

m and n are each 0;

R₃ and R₄ are independently of each other

hydrogen,

lower alkyl unsubstituted or mono- or disubstituted, especially monosubstituted, by radicals selected independently of one another from carboxy; lower alkoxy-carbonyl; and cyano;;

or

R₄ is hydrogen or -CH₃, and

R₃ is as defined above or preferably R₃ is,

acyl of the subformula R^o-CO, wherein R^o is lower alkyl; amino-lower alkyl, wherein the amino group is present in unprotected form or is protected by lower alkoxy-carbonyl;

tetrahydropyranyloxy-lower alkyl; phenyl; imidazolyl-lower alkoxyphenyl; carboxyphenyl; lower alkoxy-carbonylphenyl; halogen-lower alkylphenyl; imidazol-1-ylphenyl; pyrrolidino-lower alkylphenyl; piperazino-lower alkylphenyl; (4-lower alkylpiperazinomethyl)phenyl; morpholino-lower alkylphenyl; piperazinocarbonylphenyl; or (4-lower alkylpiperazino)phenyl;

or is acyl of the subformula R^o-O-CO-, wherein R^o is lower alkyl;

or is acyl of the subformula R^oHN-C(=W)-, wherein W is oxygen and R^o has the following meanings: morpholino-lower alkyl, phenyl, lower alkoxyphenyl, carboxyphenyl, or lower alkoxy-carbonylphenyl;

or R₃ is lower alkylphenylsulfonyl, typically 4-toluenesulfonyl;

further specific examples of preferred R₃ groups are described below for the preferred compounds of formula II,

R₅ is hydrogen or lower alkyl, especially hydrogen,

X stands for 2 hydrogen atoms or for O;

Z is methyl or hydrogen;

or a salt thereof, if at least one salt-forming group is present.

Particular preference is given to a compound of formula II wherein

m and n are each 0;

R₃ and R₄ are independently of each other

hydrogen,

lower alkyl unsubstituted or mono- or disubstituted, especially monosubstituted, by radicals selected independently of one another from carboxy; lower alkoxy carbonyl; and cyano; whereby R_4 may also be absent;

or

R_4 is absent, and

R_3 is acyl from the subformula R^o -CO-, wherein R^o is lower alkyl, especially methyl or ethyl; amino-lower alkyl, wherein the amino group is unprotected or protected by lower alkoxy carbonyl, typically tert-lower alkoxy carbonyl, for example tert-butoxy carbonyl, e.g. aminomethyl, R,S-, R-, or preferably S-1-aminoethyl, tert-butoxy carbonylaminomethyl or R,S-, R-, or preferably S-1-(tert-butoxy carbonylamino)ethyl; tetrahydropyranyloxy-lower alkyl, typically 4-(tetrahydropyranyl)oxymethyl; phenyl; imidazolyl-lower alkoxyphenyl, typically 4-[2-(imidazol-1-yl)ethyl]oxyphenyl; carboxyphenyl, typically 4-carboxyphenyl; lower alkoxy carbonylphenyl, typically 4-methoxy- or 4-ethoxy carbonylphenyl; halogen-lower alkylphenyl, typically 4-chloromethylphenyl; imidazol-1-ylphenyl, typically 4-(imidazolyl-1-yl)phenyl; pyrrolidino-lower alkylphenyl, typically 4-pyrrolidinomethylphenyl; piperazino-lower alkylphenyl, typically 4-piperazinomethylphenyl; (4-lower alkylpiperazinomethyl)phenyl, typically 4-(4-methylpiperazinomethyl)phenyl; morpholino-lower alkylphenyl, typically 4-morpholinomethylphenyl; piperazinocarbonylphenyl, typically 4-piperazinocarbonylphenyl; or (4-lower alkylpiperazino)-phenyl, typically 4-(4-methylpiperazino)phenyl;

or is acyl of the subformula R^o -O-CO-, wherein R^o is lower alkyl;

or is acyl of the subformula R^o HN-C(=W)-, wherein W is oxygen and R^o has the following preferred meanings: morpholino-lower alkyl, typically 2-morpholinoethyl, phenyl, lower alkoxyphenyl, typically 4-methoxyphenyl or 4-ethoxyphenyl, carboxyphenyl, typically 4-carboxyphenyl, or lower alkoxy carbonylphenyl, typically 4-ethoxy carbonylphenyl;

or is lower alkylphenylsulfonyl, typically 4-toluenesulfonyl;

p is 0 if R_4 is absent, or is 1 if R_3 and R_4 are both present and in each case are one of the aforementioned radicals;

R_5 is hydrogen or lower alkyl, especially hydrogen,

X stands for 2 hydrogen atoms or for O;

Z is methyl or hydrogen;

and either the two bonds characterised by wavy lines are preferably absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or also the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present.

Most especially preferred compounds of formula II are selected from;

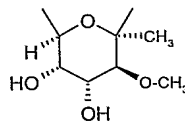
8,9,10,11-Tetrahydrostaurosporine;
N-[4-(4-methylpiperazin-1-ylmethyl)benzoyl]-1,2,3,4-tetrahydrostaurosporine;
N-(4-chloromethylbenzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-(4-(pyrrolidin-1-ylmethyl)benzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-(4-(morpholin-4-ylmethyl)benzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-(4-(piperazin-1-ylmethyl)benzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-ethyl-1,2,3,4-tetrahydrostaurosporine;
N-tosyl-1,2,3,4-tetrahydrostaurosporine;
N-trifluoroacetyl-1,2,3,4-tetrahydrostaurosporine;
N-[4-(2-imidazol-1-yl-ethoxy)benzoyl]-1,2,3,4-tetrahydrostaurosporine;
N-methoxycarbonylmethyl-1,2,3,4-tetrahydrostaurosporine;
N-carboxymethyl-1,2,3,4-tetrahydrostaurosporine;
N-terephthaloylmethyl ester-1,2,3,4-tetrahydrostaurosporine;
N-terephthaloyl-1,2,3,4-tetrahydrostaurosporine;
N-(4-ethylpiperazinylcarbonylbenzoyl)-1,2,3,4-tetrahydrostaurosporine;
N-(2-cyanoethyl)-1,2,3,4-tetrahydrostaurosporine;
N-benzoyl-1,2,3,4-tetrahydrostaurosporine;
N,N-dimethyl -1,2,3,4-tetrahydrostaurosporinium iodide;
N-BOC-glycyl-1,2,3,4-tetrahydrostaurosporine;
N-glycyl-1,2,3,4-tetrahydrostaurosporine;

N-(3-(tert-butoxycarbonyl)propyl)-1,2,3,4-tetrahydrostaurosporine;
 N-(3-carboxypropyl)-1,2,3,4-tetrahydrostaurosporine;
 N-(4-imidazol-1-yl)benzoyl]-1,2,3,4-tetrahydrostaurosporine;
 N-[(tetrahydro-2h-pyran-4-yloxy)acetyl]-1,2,3,4-tetrahydrostaurosporine;
 N-BOC-L-alanyl-1,2,3,4-tetrahydrostaurosporine;
 N-L-alanyl-1,2,3,4-tetrahydrostaurosporine hydrochloride;
 N-methyl-1,2,3,4-tetrahydro-6-methylstaurosporine;
 N-(4-carboxyphenylaminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
 N-(4-ethylphenylaminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
 N-(N-phenylaminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
 N-(N-[2-(1-morpholino)ethyl]aminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
 N-(N-[4-methoxyphenyl]aminocarbonyl)-1,2,3,4-tetrahydrostaurosporine;
 1,2,3,4-tetrahydro-6-methylstaurosporine;
 N-BOC-1,2,3,4-tetrahydrostaurosporine;
 N-BOC-1,2,3,4-tetrahydro-6-methylstaurosporine;
 N-BOC-1,2,3,4-tetrahydro-6-methyl-7-oxo-staurosporine;
 1,2,3,4,8,9,10,11-octahydrostaurosporine;
 or a pharmaceutically acceptable salt thereof, if at least one salt-forming group is present.

Most especially preferred is the compound of formula I designated 1,2,3,4-tetrahydrostaurosporine, or a (particularly pharmaceutically acceptable) salt thereof (here, m and n in formula I are 0, R₃ is hydrogen, R₄ is absent, provided no salt is present (p = 0), or is hydrogen if a salt is present (p = 1), R₅ is hydrogen, the two bonds represented by wavy lines are absent in Ring A and are replaced by a total of 4 hydrogen atoms and the two bonds represented by wavy lines in Ring B are in each case a double bond together with the parallel bonds, X stands for 2 hydrogen atoms, and Z is methyl).

Most especially preferred are the compounds of formula A wherein;

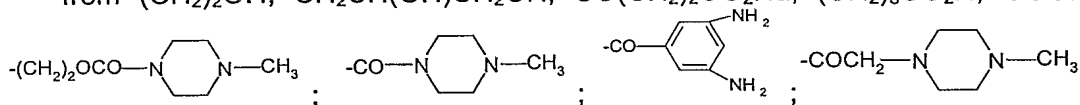
- A) X= O; R₁, R₂, R₅ = H; Q= -(CH₂)₂-O-CH(CH₂)OH-(CH₂)₂-
 B) X= O; R₁, R₂, R₅ = H; Q= -(CH₂)₂-O-CH(CH₂N(CH₃)₂)-(CH₂)₂-



- C) X= 2 hydrogen atoms; R₁, R₂, R₅ = H; Q=

Most especially preferred are the compounds of formula I wherein;

- A) X= 2 hydrogen atoms; $R_1, R_2, R_3, R_5 = H$; $R_4 = CH_3$; $Z = CH_3$ (staurosporine)
 B) X= 1 hydrogen and 1 hydroxy atoms in (R) or (S) isomeric form; $R_1, R_2, R_3, R_5 = H$; $R_4 = CH_3$; $Z = CH_3$ (UCN-01 and UCN-02)
 C) X= 2 hydrogen atoms; $R_1, R_2, R_5 = H$; $R_4 = CH_3$; $R_3 =$ benzoyl; $Z = CH_3$ (CGP41251 or PKC412 or MIDOSTAURIN)
 D) X= O; $R_1, R_2, R_5 = H$; $R_3 = CH_3$; $R_4 =$ ethyloxycarbonyl; $Z = CH_3$ (NA 382 ; CAS=143086-33-3)
 E) X= 1 hydrogen and 1 hydroxy atom; $R_1, R_2, R_5 = H$; $R_3 = CH_3$; $Z = CH_3$; and R_4 is selected from $-(CH_2)_2OH$; $-CH_2CH(OH)CH_2OH$; $-CO(CH_2)_2CO_2Na$; $-(CH_2)_3CO_2H$; $-COCH_2N(CH_3)_2$;



- F) X= 2 hydrogen atoms; $R_1, R_2, R_5 = H$; $R_3 = CH_3$; $Z = CH_3$; and R_4 is selected from N-[0-(tetrahydropyran-4-yl)-D-lactoyl]; N-[2-methyl-2-(tetrahydropyran-4-yloxy)-propionyl]; N-[0-(tetrahydropyran-4-yl)-L-lactoyl]; N-[0-(tetrahydropyran-4-yl)-D-lactoyl]; N-[2-(tetrahydropyran-4-yloxy)-acetyl]
 G) X=O; $R_1, R_2, R_5 = H$; $R_3 = CH_3$; $Z = CH_3$; and R_4 is selected from N-[0-(tetrahydropyran-4-yl)-D-lactoyl]; N-[2-(tetrahydro-pyran-4-yloxy)-acetyl]
 H) X=1 hydrogen and 1 hydroxy atom ; $R_1, R_2, R_5 = H$; $R_3 = CH_3$; $Z = CH_3$; and R_4 is selected from N-[0-(tetrahydropyran-4-yl)-D-lactoyl]; N-[2-(tetrahydro-pyran-4-yloxy)-acetyl]

The abbreviation "CAS" means the CHEMICAL ABSTRACTS registry number.

The most preferred compounds of formula I e.g. MIDOSTAURIN [International Nonproprietary Name] are covered and have been specifically described by the European patent No. 0 296 110 published on December 21, 1988, as well as in US patent No. 5,093,330 published on March 3, 1992, and Japanese Patent No. 2 708 047. Other preferred compounds are covered and described by the patent applications WO 95/32974 and WO 95/32976 both published on December 7, 1995. All the compounds described in these documents are incorporated into the present application by reference.

Most especially preferred are the compounds of formula III wherein;

- A) X= 2 hydrogen atoms; $R_1, R_2, R_5 = H$; $R_6 = CH_3$; $R_7 =$ methyloxycarbonyl; $Z = H$ (2-methyl K252a)
 B) X= 2 hydrogen atoms; $R_1, R_2, R_5, R_6 = H$; $R_7 =$ methyloxycarbonyl; $Z = H$ (K-252a)
 C) X= 2 hydrogen atoms; $R_1, R_2, R_5, R_6 = H$; $R_7 =$ methyloxycarbonyl; $Z = CH_3$ (KT-5720)

Most especially preferred are the compounds of formula IV wherein;

- A) X= O; R₁, R₂, R₅ = H; R₉= CH₂-NMe₂; R₈= CH₃ ; m'=n'=2
 B) X= O; R₁, R₂, R₅ = H; R₉= CH₂-NH₂; R₈= CH₃ ; m'=2; n'=1 (Ro-31-8425; CAS=151342-35-7)

Most especially preferred are the compounds of formula V wherein;

- A) X= O; R₁, R₂, R₅ = H; R₈= CH₃; R₁₀= -(CH₂)₃-NH₂; (Ro-31-7549; CAS=138516-31)
 B) X= O; R₁, R₂, R₅ = H; R₈= CH₃; R₁₀= -(CH₂)₃-S-(C=NH)-NH₂; (Ro-31-8220 ; CAS=125314-64-9))
 C) X= O; R₁, R₂, R₅ = H; R₈= CH₃; R₁₀= -CH₃;

Most especially preferred are the compounds of formula VI wherein;

- A) X= 2 hydrogen atoms; R₁, R₂, R₅ = H; R₄= CH₃; Z=CH₃ ; R₃ selected from methyl or (C₁-C₁₀)alkyl, arylmethyl, C₆H₂CH₂-

STAUROSPOURINE DERIVATIVES and their manufacturing process have been specifically described in many prior documents, well known by the man skilled in the art.

Compounds of formula A, B, C, D and their manufacturing process have for instance, been described in the European patents No. 0 657 458 published on June 14, 1995, in the European patents No. 0 624 586 published on November 17, 1994, in the European patents No. 0 470 490 published on February 12, 1992, in the European patents No. 0 328 026 published on August 16, 1989, in the European patents No. 0 384 349 published on August 29, 1990, as well as in many publications such as *Barry M. Trost* and Weiping Tang Org. Lett.*, 3(21), 3409-3411.

Compounds of formula I and their manufacturing processes have specifically been described in the European patents No. 0 296 110 published on December 21, 1988, as well as in US patent No. 5,093,330 published on March 3, 1992, and Japanese Patent No. 2 708 047. Compounds of formula I having a tetrahydropyran-4-yl)-lactoyl substitution on R₄ have been described in the European patent No. 0 624 590 published on November 17, 1994. Other compounds have been described in the European patent No. 0 575 955 published December 29, 1993, European patent No. 0 238 011 published on September 23, 1987 (UCN-O1), International patent application EP98/04141 published as WO99/02532 on July 03, 1998.

Compounds of formula II and their manufacturing processes have specifically been described in the European patents No. 0 296 110 published on December 21, 1988, as well as in US patent No. 5,093,330 published on March 3, 1992, and Japanese Patent No. 2 708 047.

Compounds of formula III and their manufacturing processes have specifically been described in the patent applications claiming the priority of the US patent application US 920102 filed on July 24, 1992. (i.e European patents No. 0 768 312 published on April 16, 1997, No. 1 002 534 published May 24, 2000, No. 0 651 754 published on May 10, 1995).

Compounds of formula IV and their manufacturing processes have specifically been described in the patent applications claiming the priority of the British patent applications GB 9309602 and GB 9403249 respectively filed on May 10, 1993, and on February 21, 1994. (i.e European patents No. 0 624 586 published on November 17, 1994, No. 1 002 534 published May 24, 2000, No. 0 651 754 published on May 10, 1995).

Compounds of formula V and their manufacturing processes have specifically been described in the patent applications claiming the priority of the British patent applications GB 8803048, GB 8827565, GB 8904161 and GB 8928210 respectively filed on February 10, 1988, November 25, 1988, February 23, 1989 and December 13, 1989. (i.e European patents No. 0 328 026 published on August 16, 1989, and No. 0 384 349 published August 29, 1990).

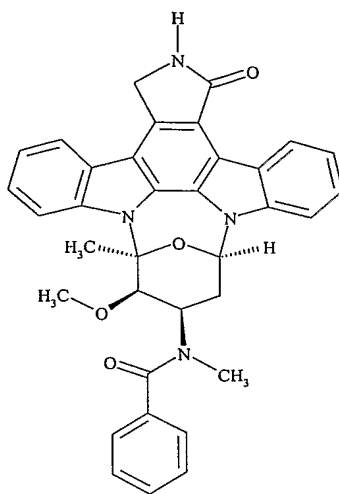
Compounds of formula VI and their manufacturing processes have specifically been described in the patent applications claiming the priority of the US patent applications 07/777,395 (Con), filed on October 10, 1991 (i.e International patent application WO 93/07153 published on April 15, 1993).

In each case where citations of patent applications or scientific publications are given in particular for the STAUROSPORINE DERIVATIVE compounds, the subject-matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to these publications.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

The preferred STAUROSPORINE DERIVATIVE according to the invention is *N*-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-*gh*:3',2',1'-*lm*]pyrrolo[3,4-*ij*][1,7]benzodiazonin-11-yl]-*N*-methylbenzamide of the

formula (VII):



(VII)

or a salt thereof, (hereinafter: "Compound of formula VII or MIDOSTAURIN").

Compound of formula VII is also known as MIDOSTAURIN [International Nonproprietary Name] or PKC412.

MIDOSTAURIN is a derivative of the naturally occurring alkaloid staurosporine, and has been specifically described in the European patent No. 0 296 110 published on December 21, 1988, as well as in US patent No. 5,093,330 published on March 3, 1992, and Japanese Patent No. 2 708 047.

CYP3A4 inhibitor of particular interest for use in the inventive combination are :

Amiodarone, Diethyldithiocarbamate, Grapefruit juice, Norfloxacin, Sertindole, Anastrozole, Diltiazem, Indinavir, Omeprazole, Sertraline, Azithromycin, Dirithromycin, Isoniazid, Oxiconazole, Troglitazone, Cannabinoids, Dusulfiram, Itraconazole, Paroxetine, Troleandomycin, Cimetidine, Entacapone, Ketoconazole, Propoxyphene, Valproic Acid, Clarithromycin, Erythromycin, Metronidazole, Quinidine, Verapamil, Clotrimazole, Ethinyl estradiol, Miconazole, Quinine, Zafirlukast, Cyclosporine, Fluconazole, Nefazodone, Quinupristin, Zileuton, Danazol, Fluoxetine, Nelfinavir, Ranitidine, Delavirdine, Fluvoxamine, Nevirapine, Ritonavir, Gestodene, Norfluoxetine, Saquinavir; preferably Amiodarone, Diethyldithiocarbamate, Norfloxacin, Sertindole, Anastrozole, Diltiazem, Indinavir, Omeprazole, Sertraline, Azithromycin, Dirithromycin, Isoniazid, Oxiconazole, Troglitazone, Cannabinoids,

Dusulfiram, Itraconazole, Paroxetine, Troleandomycin, Cimetidine, Entacapone, Ketoconazole, Propoxyphene, Valproic Acid, Clarithromycin, Erythromycin, Metronidazole, Quinidine, Verapamil, Clotrimazole, Ethinyl estradiol, Miconazole, Quinine, Zafirlukast, Cyclosporine, Fluconazole, Nefazodone, Quinupristin, Zileuton, Danazol, Fluoxetine, Nelfinavir, Ranitidine, Delavirdine, Fluvoxamine, Nevirapine, Ritonavir, Gestodene, Norfluoxetine, Saquinavir; most preferably Itraconazole

The present invention in particular provides a method of treating allergic rhinitis, allergic dermatitis, drug allergy or food allergy, angioedema, urticaria, sudden infant death syndrome, bronchopulmonary aspergillosis, multiple sclerosis, or mastocytosis, comprising administering to a mammal in need of such a treatment a therapeutically effective amount of a combination of a STAUROSPORINE DERIVATIVE and a CYP3A4 inhibitor, each in free form or in form of a pharmaceutically acceptable salt or prodrug, respectively.

Preferably the instant invention provides a method for treating mammals, especially humans, suffering from allergic rhinitis, allergic dermatitis, drug allergy or food allergy, angioedema, urticaria, sudden infant death syndrome, bronchopulmonary aspergillosis, multiple sclerosis, or mastocytosis comprising administering to a mammal in need of such treatment an therapeutically effective amount of a combination of N-[(9S,10R,11R,13R)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1H,9H-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-11-yl]-N-methylbenzamide of the formula (VI), or a pharmaceutically acceptable salt thereof and

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment, the instant invention relates to the use of a combination of a STAUROSPORINE DERIVATIVE and a CYP3A4 inhibitor, each in free form or in form of a pharmaceutically acceptable salt or prodrug, respectively, for treating allergic rhinitis, allergic dermatitis, drug allergy or food allergy, angioedema, urticaria, sudden infant death syndrome, bronchopulmonary aspergillosis, multiple sclerosis, or mastocytosis with resistance to imatinib .

In a further embodiment, the instant invention relates to the use of a combination of a STAUROSPORINE DERIVATIVE and a CYP3A4 inhibitor, each in free form or in form of a pharmaceutically acceptable salt or prodrug, respectively, for the preparation of a

pharmaceutical composition for treating allergic rhinitis, allergic dermatitis, drug allergy or food allergy, angioedema, urticaria, sudden infant death syndrome, bronchopulmonary aspergillosis, multiple sclerosis, or mastocytosis, all of these diseases and conditions also with resistance to imatinib

According to the invention a combination of *N*-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-*gh*:3',2',1'-*lm*]pyrrolo[3,4-*j*][1,7]benzodiazonin-11-yl]-*N*-methylbenzamide of the formula (VII), or a pharmaceutically acceptable salt thereof and either

or a pharmaceutically acceptable salt or prodrug thereof are the preferred combinations of a STAUROSPORINE DERIVATIVE and a CYP3A4 inhibitor.

The combination of a STAUROSPORINE DERIVATIVE and a CYP3A4 inhibitor, each in free form or in form of a pharmaceutically acceptable salt or prodrug, respectively, for treating allergic rhinitis, allergic dermatitis, drug allergy or food allergy, angioedema, urticaria, sudden infant death syndrome, bronchopulmonary aspergillosis, multiple sclerosis, or mastocytosis may be a free or fixed combination of the combination partners.

In one aspect, the present invention also relates to a combination, such as a combined preparation or a pharmaceutical composition, which comprises (a) a STAUROSPORINE DERIVATIVE, especially the STAUROSPORINE DERIVATIVE specifically mentioned hereinbefore, in particular those mentioned as being preferred, and (b) a CYP3A4 inhibitor, especially the CYP3A4 inhibitor mentioned hereinbefore, in particular those mentioned as being preferred, in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt, for simultaneous, concurrent, separate or sequential use.

The term "a combined preparation" defines especially a "kit of parts" in the sense that the combination partners (a) and (b) as defined above can be dosed independently or by use of different fixed combinations with distinguished amounts of the combination partners (a) and (b), i.e., simultaneously, concurrently, separately or sequentially. The parts of the kit of parts can then, e.g., be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. The ratio of the

total amounts of the combination partner (a) to the combination partner (b) to be administered in the combined preparation can be varied, e.g. in order to cope with the needs of a patient sub-population to be treated or the needs of the single patient which different needs can be due to the particular disease, severity of the disease, age, sex, body weight, etc. of the patients.

As mentioned above the precise dosage of the STAUROSPORINE DERIVATIVE and the CYP3A4 inhibitor to be employed for treating the diseases and conditions mentioned hereinbefore depends upon several factors including the host, the nature and the severity of the condition being treated, the mode of administration. However, in general, satisfactory results are achieved when the STAUROSPORINE DERIVATIVE is administered parenterally, e.g., intraperitoneally, intravenously, intramuscularly, subcutaneously, intratumorally, or rectally, or enterally, e.g., orally, preferably intravenously or, preferably orally, intravenously at a daily dosage of 0.1 to 10 mg/kg body weight, preferably 1 to 5 mg/kg body weight. In human trials a total dose of 225 mg/day was most presumably the Maximum Tolerated Dose (MTD). A preferred intravenous daily dosage is 0.1 to 10 mg/kg body weight or, for most larger primates, a daily dosage of 200-300 mg. A typical intravenous dosage is 3 to 5 mg/kg, three to five times a week.

Most preferably, the STAUROSPORINE DERIVATIVE, especially MIDOSTAURIN, are administered orally, by dosage forms such as microemulsions, soft gels or solid dispersions in dosages up to about 250 mg/day, in particular 225 mg/day, administered once, twice or three times daily.

Usually, a small dose is administered initially and the dosage is gradually increased until the optimal dosage for the host under treatment is determined. The upper limit of dosage is that imposed by side effects and can be determined by trial for the host being treated.

The STAUROSPORINE DERIVATIVE and the CYP3A4 inhibitor may be combined with one or more pharmaceutically acceptable carriers and, optionally, one or more other conventional pharmaceutical adjuvants and administered enterally, e.g. orally, in the form of tablets, capsules, caplets, etc. or parenterally, e.g., intraperitoneally or intravenously, in the form of sterile injectable solutions or suspensions. The enteral and parenteral compositions may be prepared by conventional means.

The infusion solutions according to the present invention are preferably sterile. This may be

readily accomplished, e.g. by filtration through sterile filtration membranes. Aseptic formation of any composition in liquid form, the aseptic filling of vials and/or combining a pharmaceutical composition of the present invention with a suitable diluent under aseptic conditions are well known to the skilled addressee.

The STAUROSPORINE DERIVATIVE and CYP3A4 inhibitor may be formulated into enteral and parenteral pharmaceutical compositions containing an amount of the active substance that is effective for treating the diseases and conditions named hereinbefore, such compositions in unit dosage form and such compositions comprising a pharmaceutically acceptable carrier.

Examples of useful compositions of STAUROSPORINE DERIVATIVE are described in the European patents No. 0 296 110, No. 0 657 164, No. 0 296 110, No.0 733 372, No.0 711 556, No.0 711 557.

The preferred compositions of STAUROSPORINE DERIVATIVE are described in the European patent No. 0 657 164 published on June 14, 1995. The described pharmaceutical compositions comprise a solution or dispersion of compounds of formula I such as MIDOSTAURIN in a saturated polyalkylene glycol glyceride, in which the glycol glyceride is a mixture of glyceryl and polyethylene glycol esters of one or more C8-C18 saturated fatty acids.

Two manufacture processes of such compositions of STAUROSPORINE DERIVATIVE are described hereafter.

Composition A:

Gelucire 44/14 (82 parts) is melted by heating to 60° C. Powdered MIDOSTAURIN (18 parts) is added to the molten material. The resulting mixture is homogenised and the dispersion obtained is introduced into hard gelatin capsules of different size, so that some contain a 25mg dosage and others a 75mg dosage of the MIDOSTAURIN. The resulting capsules are suitable for oral administration.

Composition B:

Gelucire 44/14 (86 parts) is melted by heating to 60° C. Powdered MIDOSTAURIN (14 parts) is added to the molten material. The mixture is homogenised and the dispersion obtained is introduced into hard gelatin capsules of different size, so that some contain a 25mg dosage and others a 75mg dosage of the MIDOSTAURIN. The resulting capsules are suitable for oral

administration.

Gelucire 44/14 available commercially from Gattefossé; is a mixture of esters of C8-C18 saturated fatty acids with glycerol and a polyethylene glycol having a molecular weight of about 1500, the specifications for the composition of the fatty acid component being, by weight, 4-10% caprylic acid, 3-9% capric acid, 40-50% lauric acid, 14-24% myristic acid, 4-14% palmitic acid and 5-15% stearic acid.

A preferred example of Gelucire formulation consists of:

Gelucire (44/14): 47 g

MIDOSTAURIN: 3.0g filled into a 60 mL Twist off flask

A preferred example of soft gel will contain the following Microemulsion:

Cornoil glycerides	85.0 mg
Polyethylenglykol 400	128.25 mg
Cremophor RH 40	213.75 mg
MIDOSTAURIN	25.0 mg
DL alpha Tocopherol	0.5 mg
Ethanol absolute	33.9 mg
Total	486.4 mg

However, it should be clearly understood that it is for purposes of illustration only.

It can be shown by the methods described below that the combination of a STAUROSPORINE DERIVATIVE and an CYP3A4 inhibitor compound are more effective than treatment with either of the agents alone.

Preferably, there is at least one beneficial effect, e.g., a mutual enhancing of the effect of the first and second active ingredient, in particular a synergism, e.g. a more than additive effect, additional advantageous effects, less side effects, a combined therapeutical effect in a otherwise non-effective dosage of one or both of the first and second active ingredient, and especially a strong synergism the active ingredients.

The molar ratio of STAUROSPORINE DERIVATIVE / a CYP3A4 inhibitor in the combination is generally from 1/10 to 10/1, preferably from 1/5 to 5/1, e.g. 1/2, 1/1, 2/1, or 3/1.

The treatment of allergic rhinitis, allergic dermatitis, drug allergy or food allergy, angioedema, urticaria, sudden infant death syndrome, bronchopulmonary aspergillosis, multiple sclerosis, or mastocytosis with the above combination may be a so-called first line treatment, i.e. the treatment of a freshly diagnosed disease without any preceeding chemotherapy or the like, or it may also be a so-called second line treatment, i.e. the treatment of the disease after a preceeding treatment with imatinib or a STAUROSPORINE DERIVATIVE, depending on the severity or stage of the disease as well as the over all condition of the patient etc..

The term "allergic rhinitis " as used herein means any allergic reaction of the nasal mucosa. Such allegic reaction may occur, e.g., perennially, e.g. vernal conjunctivitis, or seasonally, e.g., hay fever.

The term "allergic dermatitis" as used herein means especially atopic dermatitis, allergic contact dermatitis and eczematous dermatitis, but comprises, e.g., also seborrhoeic dermatitis, Lichen planus, urticaria and acne. Atopic dermatitis as defined herein is a chronic inflammatory skin disorder seen in individuals with a hereditary predisposition to a lowered cutaneous threshold to pruritus. It is principally characterized by extreme itching, leading to scratching and rubbing that in turns results in the typical lesons of eczema. Allergic contact dermatitis as defined herein is a form of dermatitis that is due to the allergic sensitization to various substances that produce inflammatory reactions in the skin of those who have acquired hypersensitivity to the allergen as a result of previous exposure to it.

The term "drug allergy or food allergy" as used herein pertains to an allergic reaction produced by a drug or ingested antigens, such as, for example, strawberries, milk or eggs.

The term "bronchopulmonary aspergillosis" relates to an infection of the lungs with *Aspergillus*.

The term "mastocytosis" as used herein, relates to systemic mastocytosis, for example mastocytoma, and also to canine mast cell neoplasms. Mastocytosis is a myeloproliferative disorder with limited treatment options and generally a poor prognosis. The pathogenesis of mastocytosis has been attributed to constitutive activation of the receptor tyrosine kinase KIT. In a large majority of mastocytosis patients, the deregulated tyrosine kinase activity of KIT is due to a mutation within the codon 816 of the protein (D816V) which also confers resistance to imatinib or imatinib mesylate, the latter being marketed as Gleevec® in the United States or Glivec®

elsewhere, *in vitro* and *in vivo*.

Mast cells play an important role as the primary effector cells in the allergic disorders mentioned herein. Antigen-specific IgE-mediated degranulation of mast cells leads to the subsequent release of chemical mediators and multiple cytokines and to leukotriene synthesis. Furthermore, mast cells are involved in the pathogenesis of multiple sclerosis.

Mast cell neoplasms occur in both humans and animals. In dogs, mast cell neoplasms are called mastocytomas, and the disease is common, representing 7%-21% of canine tumors. A distinction must be drawn between human mastocytosis, which is usually transient or indolent, and canine mast cell neoplasia, which behaves unpredictably and is often aggressive and metastatic. For instance, human solitary mastocytomas do not often metastasize; in contrast, 50% of canine mastocytomas behave in a malignant fashion, as estimated by Hottendorf & Nielsen (1969) after review of 46 published reports of tumors in 938 dogs.

Cancer in the pet population is a spontaneous disease. Pet owners, motivated by prolonging the quality of their animals' life, frequently seek out the specialized care and treatment of veterinary oncologists at private referral veterinary hospitals and veterinary teaching hospitals across the country. Therapeutic modalities of veterinary cancer patients are similar to humans, including surgery, chemotherapy, radiation therapy, and biotherapy. It has been estimated that there are 42 million dogs and approximately 20 million cats in the United States. Using crude estimates of cancer incidence, there are roughly 4 million new cancer diagnoses made in dogs and a similar number in cats made each year.

Cutaneous mast cell tumors in dogs are a common problem. Most mast cell tumors are benign and are cured with simple resection; however, if recurrent or metastatic to distant sites therapeutic options are limited. Treatment options for recurrent lesions can include external beam radiation therapy. For distant metastases or disseminated disease the use of Lomustine® and vinblastine containing chemotherapy protocols have demonstrated some benefit. Sites for metastases for mast cell tumors include skin, regional lymph nodes, spleen, liver, and bone marrow.

The KIT receptor's involvement in the pathogenesis of mastocytosis is suggested by the observation that several mutations resulting in constitutive activation of KIT have been detected in a number of mast cell lines. For instance, a point mutation in human c-KIT, causing substitution of Val for Asp816 in the phosphotransferase domain and receptor autoactivation,

occurs in a long-term human mast cell leukemia line (HMC-1) and in the corresponding codon in two rodent mast cell lines. Moreover, this activating mutation has been identified in situ in some cases of human mastocytosis. Two other activating mutations have been found in the intracellular juxtamembrane region of KIT, ie. the Val560Gly substitution in the human HMC-1 mast cell line, and a seven amino acid deletion (Thr573-His579) in a rodent mast cell line called FMA3.

It can be shown by established test models and especially those test models described herein that the STAUROSPORINE DERIVATIVES or in each case a pharmaceutically acceptable salt thereof, result in an effective prevention or, preferably, treatment of at least one of the diseases mentioned herein. The person skilled in the pertinent art is fully enabled to select a relevant test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects. The pharmacological activity may, for example, be demonstrated in a study as essentially described hereinafter.

Example 1

This is an open-label, randomized study to determine the clinical and pharmacodynamic effects of PKC412 in patients with acute myeloid leukemia (AML) and patients with high-risk myelodysplastic syndrome (MDS). Patients with wild type or mutated FLT3 who have not previously received a FLT3 inhibitor will be randomized to continuous twice-daily oral doses of either 50 or 100 mg

Patients will be treated until disease progression as defined by a doubling of the baseline peripheral absolute blast count, or a doubling of the bone marrow blast percentage, or an absolute blast count of $\geq 30,000/\text{mm}^3$, or the occurrence of unacceptable treatment related toxicity. All patients will be followed for one month following discontinuation of drug for Serious Adverse Events (SAE's). Patients who discontinue the study due to a study drug-related adverse event must be followed weekly for four weeks, or until resolution or stabilization of the event, whichever occurs first. Any serious adverse event occurring in a patient up to 4 weeks after stopping the trial must be reported.

Following enrollment of patients in the study under Amendment 03, an additional 12 FLT3 mutated patients will be enrolled to explore the effect of the co-administration of Itraconazole with PKC412 on the pharmacokinetic profile, safety, tolerability, and preliminary clinical efficacy.

Patients will be randomized to receive continuous twice, daily oral doses of either 50 or 100 mg to evaluate the effectiveness of PKC412 in patients with AML or MDS with wild type or mutated FLT3 in order to select a dose for further development. A dose regimen will be considered for further development if there is sufficient evidence that it has a

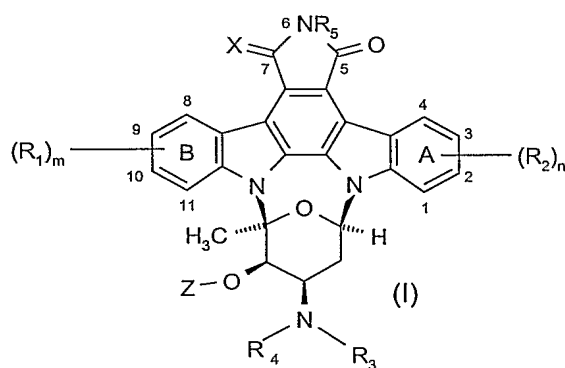
response rate greater than 20%. An overall assessment of response will be made at the end of Cycle 2, Day 28. Patients will be treated until disease progression as defined by a doubling of the peripheral baseline absolute blast count, or a doubling of the bone marrow blast percentage, or an absolute blast count of $\geq 30,000/\text{mm}^3$, or the occurrence of unacceptable treatment related toxicity. Intra-patient dose escalation of 100 mg BID daily may be permitted every 2 weeks (twice a month) for patients not demonstrating a significant reduction in the peripheral blast count or who relapse after demonstrating an initial blast reduction. In the absence of safety concerns dose escalation's of 100 mg BID daily every two weeks may continue at the discretion of the investigator until two consecutive blast counts are stabilized.

Additionally, following enrollment in the study as per Amendment 03, an additional 12 mutated FLT3 patients will be enrolled to evaluate the effects of combining PKC412 and Itraconazole on the pharmacokinetic profile, safety and tolerability profile, and preliminary efficacy. On Cycle 1 Day 1, PKC412 will be administered as a loading dose of 100 mg BID, followed by 50 mg BID of PKC412 daily for 3 weeks from Days 2-21 of Cycle 1. On Day 22 PKC412 will be administered at a dose of 50 mg BID daily in combination with Itraconazole administered orally at a dose of 100 mg BID daily orally. Itraconazole must be administered first, followed by a 5-10 minute rest interval before the PKC412 is given.

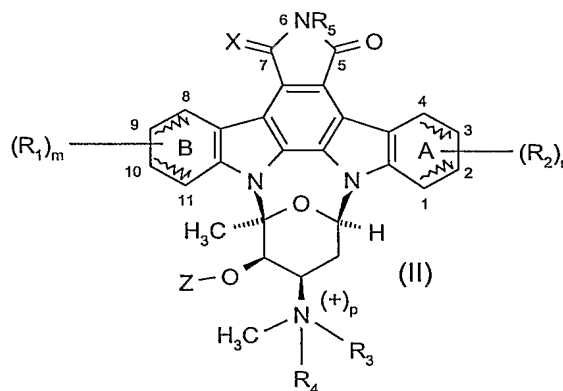
The combination of PKC412 and Itraconazole will continue until disease progression, or unacceptable toxicity. If the patient experiences unacceptable toxicity due to Itraconazole, and in the opinion of Novartis and the investigator would benefit from continued treatment with PKC412 alone, study drug may continue with intra-patient dose escalations permitted as described above.

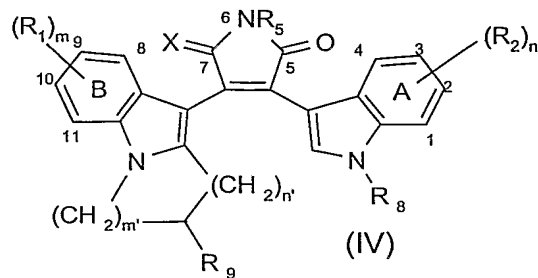
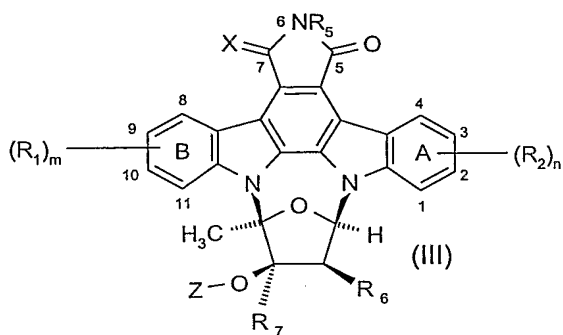
What is claimed is:

1. A method of treating myelodysplastic syndromes, lymphomas and leukemias, and solid tumors in a mammal which comprises treating the mammal in need of such treatment simultaneously, concurrently, separately or sequentially with pharmaceutically effective amounts of (a) a STAUROSPORINE DERIVATIVE, or a pharmaceutically acceptable salt or a prodrug thereof, and (b) a CYP3A4 inhibitor, or a pharmaceutically acceptable salt or a prodrug thereof.
2. The method according to claim 1 for treating acute myeloid leukemia (AML).
3. The method according to claim 1, wherein the FLT-3 inhibitor is a staurosporine derivative.
4. The method according to claim 3, wherein the staurosporine derivative is selected from the compounds of formula,



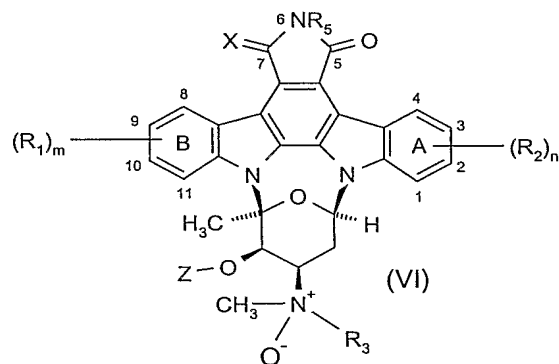
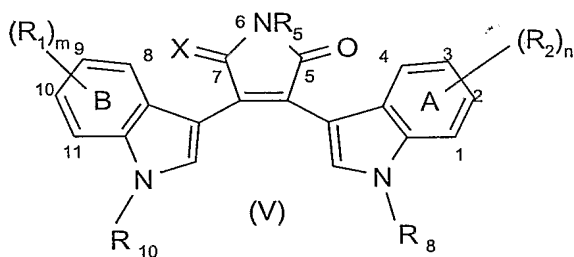
or





or

or



or

or

wherein R₁ and R₂, are, independently of one another, unsubstituted or substituted alkyl, hydrogen, halogen, hydroxy, etherified or esterified hydroxy, amino, mono- or disubstituted amino, cyano, nitro, mercapto, substituted mercapto, carboxy, esterified carboxy, carbamoyl, N-mono- or N,N-di-substituted carbamoyl, sulfo, substituted sulfonyl, aminosulfonyl or N-mono- or N,N-di-substituted aminosulfonyl;

n and m are, independently of one another, a number from and including 0 to and including 4;

n' and m' are, independently of one another, a number from and including 1 to and including 4;

R₃, R₄, R₈ and R₁₀ are, independently of one another, hydrogen, an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms in each case, a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms in each case, and in each case up to 9 heteroatoms, an acyl with up to 30 carbon atoms, wherein R₄ may also be absent;

or R₃ is acyl with up to 30 carbon atoms and R₄ not an acyl;

p is 0 if R₄ is absent, or is 1 if R₃ and R₄ are both present and in each case are one of the aforementioned radicals;

R₅ is hydrogen, an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms in each case, or a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms in each case, and in each case up to 9 heteroatoms, or acyl with up to 30 carbon atoms;

R₇, R₆ and R₉ are acyl or -(lower alkyl) -acyl, unsubstituted or substituted alkyl, hydrogen, halogen, hydroxy, etherified or esterified hydroxy, amino, mono- or disubstituted amino, cyano, nitro, mercapto, substituted mercapto, carboxy, carbonyl, carbonyldioxy, esterified carboxy, carbamoyl, N-mono- or N,N-di-substituted carbamoyl, sulfo, substituted sulfonyl, aminosulfonyl or N-mono- or N,N-di-substituted aminosulfonyl;

X stands for 2 hydrogen atoms; for 1 hydrogen atom and hydroxy; for O; or for hydrogen and lower alkoxy;

Z stands for hydrogen or lower alkyl;

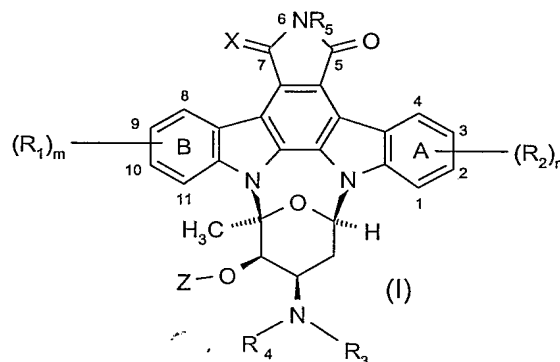
and either the two bonds characterised by wavy lines are absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present.

5. The method according to claim 3, wherein the staurosporine derivative is a staurosporin derivative of formula I,



wherein

m and n are each 0;

R₃ and R₄ are independently of each other hydrogen,

lower alkyl unsubstituted or mono- or disubstituted, especially monosubstituted, by radicals selected independently of one another from carboxy; lower alkoxy carbonyl; and cyano; or

R₄ is hydrogen or -CH₃, and

R₃ is acyl of the subformula R^o-CO-, wherein R^o is lower alkyl; amino-lower alkyl, wherein the amino group is present in unprotected form or is protected by lower alkoxy carbonyl; tetrahydropyranyloxy-lower alkyl; phenyl; imidazolyl-lower alkoxyphenyl; carboxyphenyl; lower alkoxy carbonylphenyl; halogen-lower alkylphenyl; imidazol-1-ylphenyl; pyrrolidino-lower alkylphenyl; piperazino-lower alkylphenyl; (4-lower alkylpiperazinomethyl)phenyl; morpholino-lower alkylphenyl; piperazinocarbonylphenyl; or (4-lower alkylpiperazino)phenyl;

or is acyl of the subformula R^o-O-CO-, wherein R^o is lower alkyl;

or is acyl of the subformula R^oHN-C(=W)-, wherein W is oxygen and R^o has the following meanings: morpholino-lower alkyl, phenyl, lower alkoxyphenyl, carboxyphenyl, or lower alkoxy-

carbonylphenyl;

or R₃ is lower alkylphenylsulfonyl, typically 4-toluenesulfonyl;

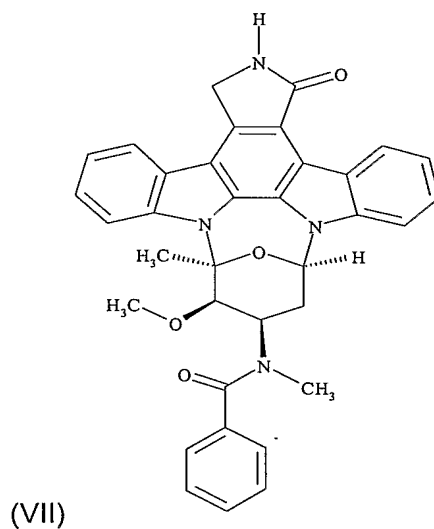
R₅ is hydrogen or lower alkyl,

X stands for 2 hydrogen atoms or for O;

Z is methyl or hydrogen;

or a salt thereof, if at least one salt-forming group is present.

6. The method according to claim 3, wherein the staurosporine derivative is *N*-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-*gh*:3',2',1'-*lm*]pyrrolo[3,4-*j*][1,7]benzodiazonin-11-yl]-*N*-methylbenzamide of the formula (VII):



or a salt thereof.

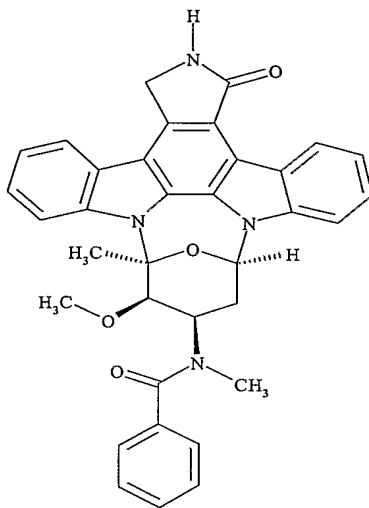
7. The method according to claim 1, wherein the

8.

15. Use of a combination of (a) a FLT-3 inhibitor and (b) a CYP3A4 inhibitor for treating myelodysplastic syndromes, lymphomas and leukemias, and solid tumors.

16. Use according to claim 15 for treating acute myeloid leukemia (AML), colorectal cancer (CRC) or non-small cell lung cancer (NSCLC).

17. Use according to claim 15, wherein the FLT-3 inhibitor is -[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2-*g*h:3',2',1'-*lm*]pyrrolo[3,4-*j*][1,7]benzodiazonin-11-yl]-*N*-methylbenzamide of the formula (VII):



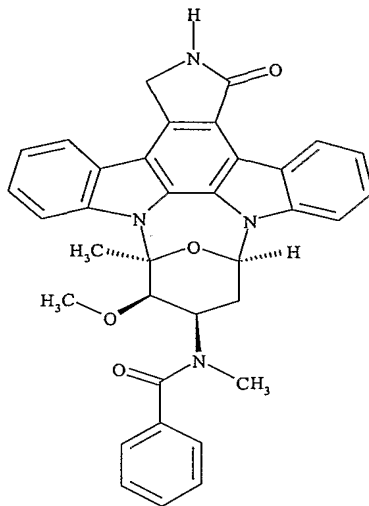
(VII)

or a salt thereof and the CYP3A4 inhibitor is selected from the group consisting of Amiodarone, Diethyldithiocarbamate, Grapefruit juice, Norfloxacin, Sertindole, Anastrozole, Diltiazem, Indinavir, Omeprazole, Sertraline, Azithromycin, Dirithromycin, Isoniazid, Oxiconazole, Troglitazone, Cannabinoids, Dusulfiram, Itraconazole, Paroxetine, Troleandomycin, Cimetidine, Entacapone, Ketoconazole, Propoxyphene, Valproic Acid, Clarithromycin, Erythromycin, Metronidazole, Quinidine, Verapamil, Clotrimazole, Ethinyl estradiol, Miconazole, Quinine, Zafirlukast, Cyclosporine, Fluconazole, Nefazodone, Quinupristin, Zileuton, Danazol, Fluoxetine, Nelfinavir, Ranitidine, Delavirdine, Fluvoxamine, Nevirapine, Ritonavir, Gestodene, Norfluoxetine, Saquinavir or, in each case a pharmaceutically acceptable salt thereof.

18. Use of a combination of (a) a FLT-3 inhibitor and (b) a CYP3A4 for the preparation of a medicament for the treatment of myelodysplastic syndromes, lymphomas and leukemias and solid tumors.

19. Use according to claim 18 for treating acute myeloid leukemia (AML), colorectal cancer (CRC) or non-small cell lung cancer (NSCLC).

20. Use according to claim 18, wherein the FLT-3 inhibitor is -[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-*gh*:3',2',1'-*lm*]pyrrolo[3,4-*j*][1,7]benzodiazonin-11-yl]-*N*-methylbenzamide of the formula (VII):



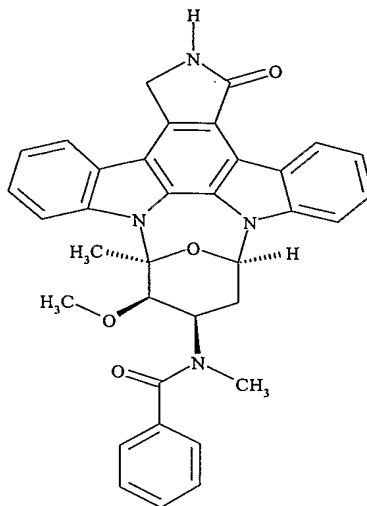
or a salt thereof and the CYP3A4 inhibitor is selected from the group consisting of Amiodarone, Diethyldithiocarbamate, Norfloxacin, Sertindole, Anastrozole, Diltiazem, Indinavir, Omeprazole, Sertraline, Azithromycin, Dirithromycin, Isoniazid, Oxiconazole, Troglitazone, Cannabinoids, Dusulfiram, Itraconazole, Paroxetine, Troleandomycin, Cimetidine, Entacapone, Ketoconazole, Propoxyphene, Valproic Acid, Clarithromycin, Erythromycin, Metronidazole, Quinidine, Verapamil, Clotrimazole, Ethinyl estradiol, Miconazole, Quinine, Zafirlukast, Cyclosporine, Fluconazole, Nefazodone, Quinupristin, Zileuton, Danazol, Fluoxetine, Nelfinavir, Ranitidine, Delavirdine, Fluvoxamine, Nevirapine, Ritonavir, Gestodene, Norfluoxetine, Saquinavir or, in each case a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising (a) a FLT-3 inhibitor and (b) CYP3A4 inhibitor for the treatment of myelodysplastic syndromes, lymphomas and leukemias and solid tumors.

22. A pharmaceutical composition according to claim 21 for treating acute myeloid leukemia (AML), colorectal cancer (CRC) or non-small cell lung cancer (NSCLC).

23. A pharmaceutical composition according to claim 21, wherein the FLT-3 inhibitor is -[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-

diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-11-yl]-*N*-methylbenzamide of the formula (VII):



(VII)

or a salt thereof and the CYP3A4 is Itraconazole, or, in each case a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/009253

A. CLASSIFICATION OF SUBJECT MATTER

A61K31/00 A61K31/553 A61K31/496 A61P35/00 A61P35/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

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Blott, C

INTERNATIONAL SEARCH REPORT

International Application No

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